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CRYPTOTROPHIC FACTORS IN NUTRITION.[1]

By EMERITUS PROFESSOR W. A. OSBORNE,
Melbourne.

THE layman often asks how our ancestors managed to do as well as they seem to have done without any of this new nutritional lore. The answer is exceedingly simple: they did badly. The historical evidence of malnutrition in the past is easily obtained. Famines were frequent; our surviving ritual of grace before meat dates from a time when the supplies of food were uncertain. Waves of ergotism swept over Europe and scurvy was endemic in the cities which were walled in after the Germanic hordes had destroyed the great Roman peace. Only a small minority of the inhabitants of any country was well fed. The Norman was a meat eater—hence his stern poaching laws—and the poorly fed Saxon had no chance in battle or rebellion; the aristocrat, owing to his better feeding, was immeasurably a better animal than the commoner; the gown youth often enjoyed a diet superior to the town youth and won easy victories in riots. After a surfeit in November, when all but breeding animals were killed, the poorer classes saw no fresh meat for nearly half a year. Moreover, agricultural methods up till the nineteenth century were backward and the foodstuffs and fodderstuffs grown were few and far below modern standards. Milk, egg and flesh yields per animal were a fraction of what we expect today. The preservation of food by canning, freezing, chilling and processing belong to our own generation. Many sidelights bring into prominence the faulty nutrition of our ancestors. I shall mention one which has a medical interest. A survey of old books on *materia medica*, herbals and the like reveals how numerous were medicines dealing with the bowels; astringents and purgatives, the latter often of a furious potency, made up the greater part of the official or home pharmacopœia. Old geographies and histories, amongst the benefits conferred on the world by the discovery of America, mention jalap as the supreme gift of the Mexican! What physician uses it today, or the squirting cucumber or gamboge? A jest has come down to us from the middle ages made by a Hebrew doctor concerning his Gentile colleagues—they resembled their own Saint Peter, for they had power to bind and to loose. I have mentioned scurvy, which was urban long before its maritime incidence became obvious. Scurvy was reduced in cities by two factors; one was the potato introduced from America, the other was gunpowder, which, by rendering city walls useless, allowed expansion into suburbs where garden plots were possible.

RECENT TRENDS IN NUTRITIONAL THEORY.

Energy of Foods.

The determination of the Calorie contents of foods was a great step forward. No doubt the importance of the Calorie value was exaggerated; but there is a possibility today that it may be under-estimated, for there are fashions in science. What should we think if one motorist said, "Look after the petrol and let the lubricating oil look after itself", whilst another proclaimed, "Take care of your lubricating oil, the petrol needs are easily detected and met"? The measurement of the energy content of foods can be carried out with exactitude, and the grim possibility must be faced that the civilian populations of some belligerent countries may be getting less than their bodies require.

Power.

The conception of the energy liberated in unit time brings in another dimension and naturally is of immense importance in engineering, but strangely enough it has not received the attention it deserves in metabolic theory. Butter has something like six times the energy content of

[1] Read at a meeting of the Victorian Branch of the British Medical Association on May 7, 1941.

gelignite, but the gelignite has the knack of letting its energy off in a fraction of a second and hence is an explosive. Protein by virtue of certain amino-acids ranks higher than the other foods from the standpoint of power, and there is reason to believe that the amino-acids concerned can act like detonators and explode other chemical groups. The daily expenditure of Calories of an ox in harness is far greater than that of a carnivore such as a tiger; but the tiger by a rapid liberation of energy kills the ox.

Food for Growth.

Casein is the ideal growth protein for the young mammal, but it is too often forgotten that casein has not the full complement of amino-acids—it is not a "complete" protein in modern parlance. The flesh of the young mammal before casein has been reinforced and supplanted by other and better proteins is different from the flesh of the adult. This is strikingly obvious to our organs of taste and general percipient faculties in eating, for veal as a food is widely different from beef and sucking pig rarely suggests pork. Those who advocate milk as a food for adults other than nursing and expectant mothers must base their arguments on vitamins rather than on the value of the protein.

Cryptotrophic Factors.

I shall limit the term "cryptotrophic factors" to those substances which in minute amounts have a marked influence on nutrition. Gross deficiencies revealed as salt hunger, lime hunger, phosphate hunger are readily understandable, and the cure is easy to prescribe. I may perhaps as an aside mention the problem of the wide prevalence of salt hunger, despite the fact that sodium chloride is the most abundant water-soluble mineral salt in the soil, as evidenced by the sea and by lakes without outlet. Animals in captivity with deficient salt in their food will often acquire the habit of drinking their urine, a habit much too prominent in zoological gardens, especially with monkeys. Iron and iodine scarcely come under the classification of cryptotrophic; but just where to place copper is a problem, for it is not like iron or iodine, a constituent of a well-known chemical agent whose function has been determined. One may divide the cryptotrophic factors into two groups: (*a*) trace elements, (*b*) vitamins.

Trace Elements.

In a wide series of researches in Russia, Britain, America and (one is glad to note) Australia and New Zealand, the importance of trace elements has been demonstrated. The addition of minute amounts of cobalt, probably in conjunction with iron, cured or prevented bush sickness in sheep; manganese cured "slipped tendon" in chickens. I am aware that these researches have not remained unchallenged, but there is, I take it, sufficient evidence that trace elements are widely operative, at least in the nurture of plants. Rice has been shown to be responsive to manganese, iron, zinc and copper in mere traces in the soil, and one may be sure that owing to the identity of cell chemistry in plant and animal a similar reaction of the animal is to be expected.[1] Just how these trace elements operate has not been worked out. Some may be co-ferments in enzyme processes. Nearly half a century ago it was discovered accidentally that the more diastase is freed from other substances, and particularly from mineral matter, the less active it becomes. Subsequent research showed that the addition of a trace of halogen could restore the activity. Until further investigations are carried out our views must remain speculative and probably miss the truth. I would venture to hazard one suggestion: I believe the clue is to be found in sea water. As A. B. MacCallum of Toronto pointed out forty years ago, the blood and body fluids of all vertebrates above the shark have a sea water basis—not the sea water of today, but the more dilute sea water of a past geological age, when the standardization of blood took place as a great forward step in evolution. This idea followed from the suggestion of Meyer and Overton that physiological saline solution, made empirically, is really sea water diluted down. We have therefore reason to expect that every element found in sea water may play a part in cytoplasmic structure or metabolism. It is interesting to note in this connexion that in an artificial sea water containing every known constituent no fish will live. Iodine may be absent from alpine and other soils, but it is present in sea water, as the high iodine content of several seaweeds shows. As gold has been found in sea water, though not in company promoters' optimistic percentages, I should not be surprised to find gold added shortly to the trace elements necessary in nutrition.

Vitamins.

We owe the term "vitamin", originally vitamine, to Casimir Funk, working under Sir Charles Martin at the Lister Institute. As is well known, the protective substance in rice polishings which prevents or cures beriberi is not an amine as Funk announced. It was a pity that such faulty chemistry should have emanated from the Lister Institute, but a still greater pity that the term "vitamine", repugnant to any true man of science, should have been allowed, for the exploitation of the term by unscrupulous commercialism must have been obvious from the first. The credit for the recognition of beriberi as a deficiency disease must be given to Gryns (1909). I can remember well the scepticism, sometimes accompanied with Homeric laughter, with which this idea was greeted by the then great authorities in tropical medicine, who brought forward many arguments to prove that beriberi was an infection. But the new doctrine prevailed. It is pleasing to observe that due credit is being paid to Sir Frederick Gowland Hopkins for the part he played in the development of our ideas on vitamins, or "accessory factors", as he named them—would that his terminology had been retained! I was privileged to see much of Hopkins in the beginning of this century, at a time when the early work on radium was appearing. The fact that radium when removed left a something behind, a mere trace of a something which could yet produce marked effects on an electroscope, attracted Hopkins as displaying some resemblance to the mere traces of a substance, present in butter but not in lard, without which young rats would not grow. Hopkins had the central idea of deficiency long before Gryns established the cause of beriberi. An animal is a mechanism made from assembled parts; if one small item is missing the whole structure and functioning suffer. The plant has amazing powers of chemical synthesis; the animal, probably owing to its parasitism, has lost this faculty. It is true that some side-chains can be detached or transposed, but no animal has power to synthesize an aromatic ring. Some thirty-four years ago I coined the term "cyclopoietic" for the ring-building plant, and "acyclopoietic" for the animal helpless in this regard. It may be stated with assurance that every ringed chemical group wanted in the animal body must be found already formed in the food.

I should like here to point out how much in the tradition and usages of animal breeders and fanciers is explainable by our modern knowledge. For untold years it has been known that chickens must be reared on the ground; they pine and die if brought up on flooring. Parrots in captivity often take to coprophagy; this habit is cured at once if they are given capsicum, which as we know is rich in vitamin *C*. The administration of linseed oil to horses to produce an improved coat has been a long time in operation, and now linoleic acid is classified as vitamin *F*. Much of the success of the Dublin Zoo in breeding healthy lions has been due to the simple procedure of giving the beasts a whole animal to eat and not merely bone and skeletal muscle; we now know that with the exception of the pig, skeletal muscle is singularly low in vitamin content, whereas glands are high.

What functions do vitamins perform in the animal economy? Alas, we know only a small part of the story. Firstly, as stated, they may be integral parts of cell structure. Astonishment has been expressed at the number of parts which have to be manufactured and assembled to

[1] See, for example, "Effects of Certain Cryptotrophic Elements upon the Growth and Yield of Upland Rice", by Esteban Y. Castillo, *The Philippine Agriculturist*, Volume XXIX, Number 10, March, 1941; also "Role of Molybdenum in Plant's Development", by E. V. Bobko and A. G. Savvina, *Comptes rendus (Doklady)*, Volume XXIX, Number 7, 1940.

make a Bren gun which, compared with a cell nucleus, is simplicity itself. Again, they may be hormone precursors. In 1905 I published an address entitled "Cheap Foods and Wholesome Foods", and in it I ventured on the following suggestion:

Recent physiological research has shown that there exist in natural foods small traces of chemical substances which are of immense importance to the body. Many organs in order that they should act at the proper times and with the proper intensities are stimulated by means of chemical messengers or hormones which come to them in the blood stream. It is highly probable that the body is dependent for its supply of hormones on certain chemical substances which are present in food though only in very small amounts. Hence it is that many patent articles and special preparations of natural foods may be injurious through their very purity.

Vitamins may also act as catalysts or co-catalysts. The suggested relation of a respiratory enzyme and of the extrinsic blood-building factor in food to vitamins has recently been discussed.

Australia, developing her own manufactures, when free importation is crippled by war conditions, is finding how many key substances there are in each process without which success is impossible or at least difficult. Vitamins resemble in certain respects these key materials. It would serve no useful purpose if I attempted to give here an exhaustive list of the vitamins with their occurrence, constitution, action and dose; this information can now be easily obtained in well-known textbooks and in advertising literature published by reputable food firms. The time is surely coming when we shall give up the alphabetic nomenclature and refer to the chemical name, unless this is too polysyllabic, in which case an easily recognized curtailment could be used.

I come now to the exaggerated claims made for vitamins, not only by those commercially interested, but by members of the profession and by certain physiologists. I need hardly waste time in referring to the preposterous statements which are sent over the air by interested persons and by faddists. At one time the broadcast information on food was given in Melbourne by a geologist; but he at least had a scientific training and appreciated the value of accuracy, though the subject was remote from his specialty. But the public are now receiving distorted information on vitamins from professors of plausibility and experts on humbugging. It is high time that the profession of dietitian was legally registered and the public thereby protected in health and pocket from alleged dietetic practitioners who are salesmen and nothing else. I wish, however, to stress the fact that those who are rightly regarded as authorities are sometimes carried away by uncritical enthusiasm. First, there is the relation of dental caries to deficiency in vitamin *D*. That decay of the teeth can be precipitated and aggravated by *D* avitaminosis is now beyond the trajectory of criticism; but what I object to is the very common inference that there will be no caries if vitamin *D* is abundant in the diet, and conversely, that tooth decay is to be regarded as evidence of lack of this vitamin. Let me remind you of a universal law of biology, which tells us that every organ is subject to degeneration and will be retained by the species only if its presence confers an advantage in the struggle for existence. Before dental science and craftsmanship attained their present high standards deficient teeth meant deficient nutrition, except in those few cases in which abnormally hard gums allowed mastication. Further, the girl with dental caries, especially incisor caries, was sexually unattractive or actually sexually repellant. Two powerful agents in evolution were therefore at work to eliminate the tendency to dental decay. Today, thanks to the dental art, mastication and digestion are normal in the edentulous, and the toothless girl can be as winsome as her full-toothed sister. This view which I have put forward at various times has been challenged; but I would ask my critics two simple questions: Do you regard teeth as exceptional in that they are immune to degeneration? And secondly, do you regard the edentulous as equal in masticatory power and in digestion generally to the full toothed? The sexual selection factor I find generally admitted. No one as yet has attributed the blindness of fish living in underground streams to the absence of vitamin *A*; but such is the force of an uncritical attachment to a darling doctrine that I have no doubt that this preposterous idea will be seriously put forward. The merciless law of natural selection has weeded out degenerate eyes in fish living in illuminated water; but in cave streams the presence of eyes conferred no advantage and so degeneration became cumulative. If my contention is correct, human teeth are destined to go the way of the snake's legs.

My next example of an exaggerated claim for vitamins is the vigorous propaganda for wholemeal bread. I am not giving you an opinion nor a conjecture, but a fact which you can verify by consulting any miller, when I state that a bread made from wholemeal flour without any alteration to its constituents would be heavy, unpalatable and indigestible. What is usually done is to separate the germ, treat this by heating, and add some of it back to the flour. Another point is that unless exceptional pains are taken with the grinding of the pericarp, the bran may be irritating to the intestine and indeed may produce bleeding from the mucous membrane of the colon. That bran is irritating to the intestine is known to animal breeders and trainers. A few handfuls of bran in the feed can change the discrete, spheroidal excrement of the horse into a pultaceous mass of bovine suggestion. With many persons a genuine wholemeal bread will race through the intestines, greatly lowering absorption. Before a doctor or dietitian prescribes wholemeal bread he should inquire whether the flour is actually wholemeal and whether the prospective consumer is likely to suffer from colonic scarification. Advocates of wholemeal bread should also be prepared to explain why wheat should be toxic to some animals. A horse which has had access to a bag of wheat develops laminitis and usually dies. Mere distension of the gut cannot explain the condition, which has obviously a toxic origin. Preponderance of wheat, I am told, adversely affects poultry.

My third instance is the relation of night blindness to deficiency of vitamin *A*. The simple fact is that one of the first indications of *A* deficiency to appear is loss of crepuscular vision; but it would be grossly illogical and erroneous to ascribe any difference in night vision to a difference in vitamin *A* intake. A boy who has been brought up in a country environment without artificial lighting will retain throughout life the ability to move about in low illumination, and it would be ridiculous to ascribe this to abundance of vitamin *A*.

Lastly, there is a very real danger that in our enthusiasm for protective foods in childhood we may neglect other factors remote from diet. Experience with evacuees in England has brought home the fact that deficient sleep due to vermin or overcrowding or late hours will keep children undersized, no matter how much vitamin is added to the diet.

The question, and it is an important one, is very prominent today whether synthetic vitamins can take the place of those occurring naturally. This is indeed a thorny matter, and I dare not hazard a prophecy which way humanity will choose to go. A natural source has been likened to crude opium, which varies in its alkaloidal content, and which the modern physician rarely prescribes. On the other hand, there is always the possibility that what we regard as a single vitamin in a foodstuff may be a complex vitamin with reciprocal reinforcement or syngerism amongst its constituents. I should be inclined to think, though I am open to correction and conviction, that the preponderating attitude today amongst experts is in favour of the naturally occurring vitamins.

Whatever happens to the vitaminizing of foods, I sincerely hope that British and Australian folk will not become food-conscious. I never find myself in the company of food faddists without thinking of the Venerable Bede's remark that much of the sadness of hell is having to listen to the discourse of devils. The vegetarian is always with us, "full of wind and self-righteousness", as Sir Robert Hutchison has put it. Nature has ordained that pleasure should dictate our choice of food and then, of course, instinct is always operative. Instinct makes us find canned meat unpleasant after a few days' exclusive use; instinct

makes us salt a vegetable soup so that it becomes isotonic with the blood and gastric cells. Some of the strongest instincts have as yet no scientific explanation. We avoid eating the flesh of a cow, ewe or sow recently parturient, or of a fish which has spawned; but though there is no biochemical explanation for this, we may be sure that it is wise. The fat of river fish we do not relish; but analytic chemistry will not tell us why. And I would respectfully say to wholemeal enthusiasts that the higher pleasure given by white bread may not be a perversion, but may one day be linked up with some attribute of food hitherto unrecognized. I do trust that British sanity and common sense and the absence of crowd psychology will be retained in our nutrition. I am a great admirer of the United States of America; but I confess that I there find food faddism rather too prominent. On one of my visits everyone was eating yeast, a few years later it was raw cabbage, then came a vogue of tomato juice, and on my next visit everyone will, I suppose, be chewing sawdust. A happy medium between what pleasure indicates and science prescribes will, I take it, be our dietetic fate, and this should apply particularly to the application of vitamin theory.

THE USE OF POOLED HUMAN SERUM FOR THE TREATMENT OF HÆMORRHAGE AND SHOCK.[1]

By MARJORIE BICK and E. B. DREVERMANN.

(From the Walter and Eliza Hall Institute, Melbourne.)

AT the present time much attention is focused on the treatment of hæmorrhage and shock, particularly by means of the infusion of human serum.

In 1918 Peyton Rous and Wilson[1] first suggested the use of serum for this purpose, and showed that in animals, the concentration of hæmoglobin per 100 cubic centimetres of blood could be reduced to below 30% of the initial value without grave disability, providing that the loss of blood volume was replaced by serum of the same species. This work was confirmed more recently by Levinson, Neuwelt and Necheles,[2] and by Magladery, Solandt and Best.[3] The value of serum in the treatment of shock in animals has been demonstrated by Best and Solandt[4] and by Bond and Wright.[5] Each of these observers has shown that in the treatment of hæmorrhage, infusion of serum is, within limits, little inferior to that of blood, while the results obtained in the treatment of shock by serum administration were at least as satisfactory as those obtained by blood transfusion.

Although so much experimental work has been completed, little has been published on the use of serum for human patients suffering from these conditions. The following investigations were therefore carried out in an attempt to ascertain the value of the administration of serum in the treatment of those patients, both in its original form and after it had been dried and reconstituted, and to determine whether its use would be followed by any untoward reactions.

Methods.

Collection of Blood and Preparation of Serum.

Placental blood was collected by the method described by Hawkins and Brewer;[6] but the absence of any firm clot even on the addition of calcium chloride and thrombokinase, and the small average yield of 20 cubic centimetres for each placenta, forced us to abandon it as a method of obtaining blood for the preparation of serum. Blood was therefore obtained from donors of the Red Cross Transfusion Service. It was withdrawn aseptically from the median cubital veins and collected into sterile standard "Soluvac" transfusion flasks without the addition of any anticoagulant. After having stood for five or six hours to allow clotting and retraction of the clot to take place, the blood was placed in a refrigerator at 2° to 4° C., and on the following day the separated serum was transferred aseptically to Erlenmeyer flasks by means of sterile pipettes. The bulk of the serum thus obtained was free from erythrocytes. The clot was then replaced in the refrigerator and the procedure was repeated on the second or third day after collection. Erythrocytes were removed from the serum collected on the second and third days by centrifugalization; but it was found that this was unnecessary with the serum collected on the first day, as the few erythrocytes present could be left to form a sediment without any risk of hæmolysis. Blood of the four groups was collected; but the serum from each donor was kept separate until 1,800 cubic centimetres of serum were obtained. The serum was then pooled and drawn through a Seitz E.K. filter pad, the exit of the filter being fitted with a double "T" piece, so that 600 cubic centimetres of serum could be diverted into each of three sterile "Soluvac" transfusion flasks. Some of the serum used was prepared for us by the Commonwealth Serum Laboratories by a method described by Morgan.[7] To this serum merthiolate was added to a concentration of one in 10,000.

The Preparation of Dried Serum.

An attempt was made to dry serum by the method described by Edwards, Kay and Davie;[8] but we found that a much higher temperature than 37° C. was required to produce even slow drying, and that the method was unsatisfactory in that leakage in the apparatus occurred even when the most careful precautions were taken. A modification of Martin's[9] original method was therefore adopted.

The apparatus used (illustrated in Figure I) consisted of a round-bottomed flask (*B*) of 1,000 cubic centimetres capacity, fitted with a number 4 "Pyrex" ground glass joint (*a*), the flask being connected by a similar joint (*b*) to a copper flask (*C*), which in turn was connected to a water pump by the outlet (*F*). This latter flask was immersed in an ice bath and served as a condenser. Serum to be dried, after

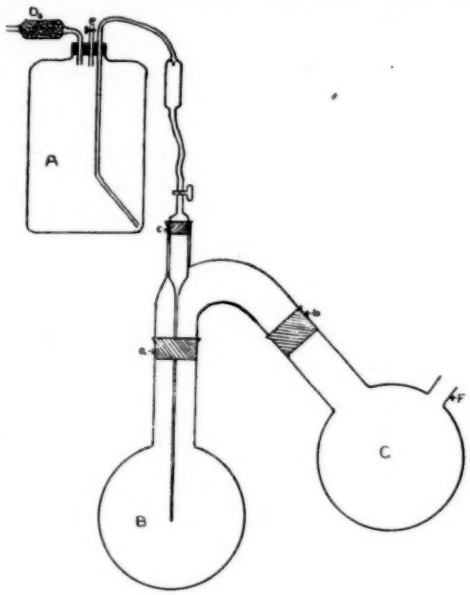

Fig I.

FIGURE I.

Apparatus used for drying of serum. *A*: "Soluvac" bottle, into which serum is filtered through (*c*). *B*: 1,000 cubic centimetre "Pyrex" flask immersed in water bath at 37° C. *C*: Copper condenser immersed in ice bath. *D*: Filter packed with cotton wool. *F*: Exit to filter pump. (*a*), (*b*) and (*c*): ground glass joints.

[1] This work was done with the aid of a grant from the National Health and Medical Research Council.

TABLE I.
The Administration of Wet Serum.[1]

Case Number.	Condition.	Volume of Serum Given. (Cubic Centimetres.)	Age of Serum Given. (Days.)	Concentration of Protein in Serum Given. (Percentage.)	Concentration of Protein in Serum of Patient. (Percentage.)		Blood Pressure. (Millimetres of Mercury.)		Pulse. (Beats per Minute.)		Hæmoglobin Value. (Percentage.)		Reaction.
					Before.	After.	Before.	After.	Before.	After.	Before.	After.	
I	Inoperable carcinoma	600	60	7·0	5·3	5·9							Transient urticaria.
II	Hæmatemesis	600	42	5·4	4·1	4·7	95	105			63	59	Temperature 100·4° F.; twelve hours later œdema disappeared.
III	Hæmatemesis	600		7·0	6·0	6·1	100	120	132	120	46	30	No reaction.
IV	Post-operative hæmorrhage and shock.	1200	42	6·2	5·5	6·0	Immeasurable.	120			94	85	No reaction. Death several days later.
V	Shock	600			6·3	6·5	80	120					No reaction.
VI	Severe shock	600		6·9	5·3	5·4	Immeasurable.	35					Death after administration.
VII	Spinal injury	600		7·4	6·8	7·4			Impalpable.	60			No reaction. Great general improvement.
		600 (dried)		5·9									
VIII	Empyema; peripheral circulatory failure.	600		6·1	5·5	6·1	70	70					No reaction.
IX	Post-operative shock	600		5·8	5·8	6·9	75	100					No reaction.
X	Pseudo-hæmophilia	600		6·5	7·3	8·0							No reaction.
XI	Patient moribund on admission to hospital.	600	15										Death during infusion.
XII	Burns, shock	600	42										Slight rigor at commencement, considerable improvement.
XIII	Bitumen burns	600	16	7·1	5·4	6·5							No reaction. Great clinical improvement.
XIV	Multiple fractures, shock ..	600	21										No reaction. Great clinical improvement.
XV	Post-operative shock following lobectomy.	1200	18	6·8	6·2	6·8							No reaction.
XVI	Post-operative low protein concentration.	600	34	7·0	5·3	5·8			126	112			No reaction.
XVII	Hæmatemesis	600	23	7·3	4·7	5·4							No reaction.
XVIII	Hæmatemesis	600	25	7·1	6·4	6·8							No reaction.

[1] The serum used in the first ten cases was prepared at Commonwealth Serum Laboratories; that used in Cases XI to XVIII was prepared at the Walter and Eliza Hall Institute.

filtration into bottle *A*, passed into the flask *B* by means of a tap of one millimetre bore, and a fine capillary tube, so that as it entered the small droplets were immediately broken by the negative pressure. The temperature of flask *B* was maintained by a water bath at 37° C. Prior to use, the various parts of the apparatus were autoclaved separately and then sealed together with sterile grease. When the serum proteins appeared dry, dry air was admitted through the filter by the inlet (*D*), the condenser was emptied and the apparatus was then connected to a mercury pump for thirty minutes. The apparatus was then disconnected and the flask *B* was closed by a sterile rubber or cotton wool stopper. With this apparatus serum was dried at the rate of 80 to 90 cubic centimetres per hour.

Storage of Serum.

Serum in its original form was in some cases stored at room temperature as indicated in Table I; in the remainder it was kept in a refrigerator at 2° to 4° C. Dried serum was stored in the dark at room temperature.

FIGURE II.
Apparatus for sterilization of water used in reconstitution of dried serum.

The Administration of Serum.

Liquid serum was administered through a vein either in the leg or in the arm through the standard "Soluvac" transfusion fitting. Dried serum was reconstituted by the admission of distilled sterile water to the flask by the apparatus shown in Figure II. This was sterilized with a paper cover over the hood. The latter was removed when the flask containing water was inverted on a stand immediately prior to use. A new stopper perforated by an air vent and a glass tube connected to a standard transfusion fitting was then placed in the flask containing the reconstituted serum, which was then administered in the usual manner. Reconstitution was aided by the immersion of the flask in a water bath at 37° C.

Analysis.

The concentrations of protein in the serum and in the plasma obtained from the patients before and after the infusion were determined by the method described by Bick and Wood.[10]

Results.

Table I shows the results of administration of liquid serum to 18 patients. For obvious reasons full data of the patient's condition could not be obtained in all cases, particularly when the patient was suffering from injury to the arms. In those cases of shock or hæmorrhage a decided improvement occurred, except in Cases VI and XI, in which death occurred immediately after or during the infusion. In the remaining 16 cases there was one severe reaction in the form of a slight rigor, while two minor reactions occurred; one took the form of a very transient urticaria, which was discovered only by accident and lasted for little more than one hour, and the second was a mild temperature reaction which may have been due to other causes.

Table II shows the results of the administration of reconstituted dried serum to 11 patients suffering from shock and hæmorrhage and to eight other patients, including three suffering from subacute nephritis and two with pseudohæmophilia. Death occurred in one case of shock (Case IX) immediately after the infusion, while there was no improvement in Case IV. In the remaining nine cases clinical improvement occurred. In one of these cases the patient had a slight rise in temperature on the following day, which may have been due to the serum or to other conditions. Of the remaining patients, one suffering from subacute nephritis showed a rise in temperature twelve hours later. The serum was in this case reconstituted to half the original volume.

Serum was given prior to tooth extraction to two patients suffering from pseudohæmophilia. One patient (Case XV) had no bleeding afterwards; but the second (Case XIV) suffered a severe hæmorrhage. The effect of serum infusion on patients suffering from subacute nephritis with œdema was inconclusive.

The invariable rise in the serum protein level of the patients indicates that the protein of the infused serum remained in the circulating blood.

Discussion.

The advantages of the use of stored serum as compared with the use of stored blood have been indicated repeatedly and it is necessary only to mention them here. They may then be briefly summarized as follows: (*a*) In emergency it is unnecessary to determine the patient's blood group. (*b*) Serum in the natural state will keep for much longer periods than stored blood, and dried serum will probably keep indefinitely. (*c*) It is unnecessary to keep the serum at refrigerator temperature. The advisability of administering large volumes of serum is, however, still open to question, as numbers of observers have reported severe reactions following serum infusion. Brodie[11] reported occasional reactions in cats transfused with cat serum, and more recently Buttle, Kekwick and Schweitzer[12] have confirmed this finding. Strumia, Wagner and Monaghan[13] state that similar reactions commonly occur when 50 to 100 cubic centimetres of homologous serum are given by transfusion to human patients. This latter observation is, however, not borne out by experience in Australia in the treatment of poliomyelitis by the intravenous administration of serum.

TABLE II.

The Administration of Reconstituted Dried Serum.

Case Number.	Condition.	Volume of Serum Given. (Cubic Centimetres.)	Age of Serum Given. (Days.)	Concentration of Protein in Serum Given. (Percentage.)	Concentration of Protein in Serum of Patient. (Percentage.)		Blood Pressure. (Millimetres of Mercury.)		Pulse. (Beats per Minute.)		Hæmoglobin Value. (Percentage.)		Reaction.
					Before.	After.	Before.	After.	Before.	After.	Before.	After.	
I	Inoperable malignant disease	400	2	6·2	6·7	7·5	108	120					No reaction.
II	Hæmatemesis	400	4	7·6	6·8	7·3	95	114					No reaction.
III	Hæmatemesis	600	6	7·8	4·8	5·7	110	110					No reaction.
IV	Hæmatemesis	600	13	7·7	6·0	6·2	80	104	120	90	54	45	Bleeding continued.
V	Hæmatemesis	600	15	7·4	4·7	5·6	90	100			60	55	No reaction.
VI	Hæmatemesis	600	21	6·1	5·8	6·5	Immeasurable.	90		120			No reaction.
VII	Traumatic amputation.	600	8	7·2	6·1	6·4		120					Temperature 100° F.; signs in chest two days later.
		600 (blood)											
VIII	Severed femoral artery.	600	19	7·5	5·8	6·4	80	104					No reaction.
IX	Multiple injuries.	600	12				80	35					Death.
X	Bullet wound in abdomen.	600	36	7·3	5·1	6·3	92	118	65	85			No reaction.
		600 pre-operatively											
		600 post-operatively	14	7·1	6·0	6·4	90	120					No reaction.
XI	Shock	600	42	6·2	6·2	7·9	110	120	140	100			No reaction.
XII	Traumatic chest injury.	600	15	7·4	5·6	6·8							No reaction.
XIII	Empyema, peripheral circulatory failure.	600	15	7·5	4·9	5·9	116	150					No reaction.
XIV	Pseudohæmophilia	600	15	7·5	6·8	7·3	100	135					No reaction.
XV	Pseudohæmophilia	600	25	6·0	7·4	8·8							No reaction.
XVI	Œdema	600	10	6·7	4·6	5·1							No reaction.
XVII	Nephritis and œdema	300 (concentrated serum)	11	13·0	4·5	6·5							Temperature rose to 100° F. in 12 hours. Œdema lessened.
XVIII	Nephritis and œdema	300 (concentrated serum)	7	14·2	5·0	6·6							No reaction.
XIX	Œdema, uræmia	300 (concentrated serum)	8	12·3	4·9	6·0							No reaction.

Amberson,[14] in his review of blood substitutes, has gathered together the observations of many workers, which indicate that various pharmacologically active substances may be present in the serum. He states that freshly prepared serum may cause death from intravascular pressure, but the constituent which causes this effect disappears within half an hour after the preparation of the serum. Other more persistent substances have been described by various workers. These substances diminish during the aging of the serum and vary in amount according to the method of preparation.

Reactions may be due to three factors: (i) bacterial contamination of the infused fluid, (ii) incompatibility between the serum and the blood of the recipient, (iii) the production of injurious substances in the preparation of the serum. The first of these factors may be overcome by strict aseptic precautions. The second factor is probably of importance only when concentrated serum is given in large amounts, and may account for the reactions reported by Aldrich, Stokes, Killingsworth and McGuinness[15] to have occurred after the treatment of nephrosis by the infusion of concentrated serum. The recent work of Bryce and Jakobowicz,[16] however, has indicated a method by which serum may be pooled so that the resultant titre is very low. The third factor is likely to be troublesome only when very large doses of serum are administered, and may be eliminated by the clotting of the plasma at a low temperature in the absence of red blood cells.

In our results three deaths are recorded as having occurred during or immediately after infusion. In these cases (Cases VI and XI in Table I and Case IX in Table II) the degree of shock and the extent of the injuries were so great that it is unlikely that any treatment would have been of any avail. Excluding these cases, we observed mild reactions in only three of sixteen cases in which serum in its natural state was administered, and doubtful reactions occurred in only two of 18 cases in which reconstituted dried serum was given.

In the limited series the incidence of reactions was not higher than after transfusion of fresh blood from donors of the Victorian Red Cross Blood Transfusion Service. It must be stressed, however, that the largest volume of serum given was 1,200 cubic centimetres, and that in larger quantities the vasotonin described by Amberson[14] may be present in such an amount as to prove injurious.

Although Buttle, Kekwick and Schweitzer[12] have demonstrated in cats that the infusion of plasma does not result in reactions, we have used serum because of the possibility that plasma in transport may clot through being shaken. It is also easier to ensure the sterility of serum, since it readily passes through a Seitz bacterial filter pad, whereas plasma clots during filtration.

The method we have used for drying serum is not recommended for the production of large quantities, as it is very slow and the product is yellowish and coarsely granular; moreover, a small portion of the protein is denatured, so that after reconstitution, which takes from fifteen to twenty minutes per pint, the fluid is turbid. It is, however, an inexpensive practical method of producing experimental quantities. This turbidity can be removed only by passing the reconstituted serum through a Seitz bacterial filter pad; this shows that the particles are exceedingly small. The methods of Esler, Thomas and Steffen[17] of Flosdorf and Mudd,[18] and of Greaves and Adair[19] produce a much finer dried serum which is more readily reconstituted. Serum may be concentrated prior to being dried by the method of Thalhimer.[20]

The question arises as to when serum infusion shall be used in the treatment of shock or hæmorrhage. Johnson and Blalock[21] have shown experimentally that the loss of whole blood is usually tolerated better than is the loss of an equal amount of plasma. It may therefore be assumed that serum infusion is of greater value than blood transfusion in the treatment of shock, in which a loss of plasma from the circulating blood occurs. In the treatment of hæmorrhage replacement of the blood volume by the transfusion of fresh blood is, of course, the best treatment; but in many cases blood is not otainable immediately, and previously the usual practice has been to administer saline solution while fresh blood is being obtained. The effect of serum infusion is to raise the blood pressure and to maintain this rise, while the effect of the administration of saline solution is transient. We would, therefore, advocate the intravenous administration of serum as the immediate treatment in all cases of hæmorrhage in which fresh blood is not immediately obtainable. It must be realized that in such cases serum infusion does not replace blood transfusion, but is merely a useful adjunct to the immediate treatment.

Conclusions.

From the results given it is seen that serum, either in its natural form or in the dried state, is of value in the treatment of shock or hæmorrhage, and that in a limited series of cases untoward reactions were no more common than those following the transfusion of fresh blood.

Serum infusion should be used in all cases of shock in which little blood has been lost. In the treatment of hæmorrhage serum should be administered immediately, while later further treatment may consist of blood transfusion.

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THE USE OF POOLED HUMAN SERUM IN EXPERIMENTAL PERTUSSIS.

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RECENT papers by Meyers[1] and Gepp[2] have been valuable reminders of the serious consequences in Australia of whooping cough during the first year of life. Both these authors give figures which show that pertussis is now, among young children, a more potent cause of death than diphtheria.

Large-scale clinical trials in the United States of America[3][4][5][6] have demonstrated the value of active immunization by large doses of *Hæmophilus pertussis* (Phase I) vaccine prior to exposure to infection. Sauer[7] considers that the optimum time for such immunization is in the second half-year of life. As infants are susceptible from birth, the benefit of an effective means of protection for those exposed to infection is obvious. Sauer,[8] after a review of the literature, has made the following statement: "Passive immunity, according to various investigators, occurs when intimately exposed infants are promptly injected with convalescent or hyperimmune serum before the paroxysmal stage." Cohen and Lapin[9] reported favourable results in children intimately exposed to infection by the administration of 20 to 40 cubic centimetres of serum taken from persons giving a history of pertussis.

There are many difficulties in maintaining adequate supplies of human convalescent or "hyperimmune" serum. The investigations recorded in this paper were undertaken to see if there was an experimental basis for the use of pooled normal adult serum as a prophylactic against whooping cough in young children.

Passive immunity in experimental pertussis has not been extensively studied. Powell and Jamieson[10] and Mishulow *et alii*[10] have tested human convalescent serum against infection in mice with *Hæmophilus pertussis* by the intraperitoneal route. The last-mentioned authors increased the virulence of the infecting organisms by suspending them in 4% mucin solution, and they showed definite protective powers in the majority of the specimens of serum tested. The protective action of human serum against pulmonary infection caused by *Hæmophilus pertussis* in mice has been investigated at the Commonwealth Serum Laboratories.[11] Protective antibody was shown to be present in the serum of some adult contacts of whooping cough patients, of some child convalescents and of children immunized with *Hæmophilus pertussis* (Phase I) vaccine. These antibodies were found to be active against both small and large infecting doses. Normal human serum was not found to afford protection against rapidly lethal infections, and the present paper deals with the effect of such serum against sublethal infections. This technique had not been used in our previous tests on normal human serum.

Methods.

A method of infecting mice has been described by Burnet and Timmins.[12] It consisted of instilling a suspension of living organisms into the nostrils of the animals under light general anæsthesia.

The remainder of the technique used by us was similar to that previously described.[11] The criterion of protective power of serum was the prevention of lung infection in mice given intranasally a sublethal infecting dose of *Hæmophilus pertussis*. The experimental results have been evaluated statistically.

Serum.—Serum was given by the intraperitoneal route about four hours before the infecting dose. The amount used was 0·25 or 0·3 cubic centimetre as in previous experiments. The types of serum used were as follows: (*a*) pooled normal human serum: samples were obtained at random from six batches of such serum held in stock at these laboratories; (*b*) adult contact serum ("A.C.8"): this is a highly potent serum used as a reference standard previously;[11] (*c*) normal rabbit serum: this was heated to 56° C. for thirty minutes before use.

Examination of Lungs.—The mice were killed by coal gas seven days after the infecting dose. The cut surface of the lower lobe of each lung was rubbed on a Bordet-Gengou plate. The plates were examined after three days' incubation and the degree of infection was graded arbitrarily as follows:

4 = confluent growth.
3 = semi-confluent growth.
2 = numerous discrete colonies (5 to 30 colonies per field of plate microscope magnification × 12).
1 = occasional colony.
0 = no *Hæmophilus pertussis* colony.

Strains of Hæmophilus Pertussis.—Two strains "E.O." and "P58" were used. Both were isolated from cases of whooping cough during the autumn of 1940 and both showed Phase I characteristics. They have been maintained on Bordet-Gengou medium and subcultured weekly. Strain "P58" has, in our hands, proved more virulent for mice when given intranasally than has "E.O."

Preparation of Suspensions.—The growth from a twenty-four-hour culture on a Bordet-Gengou slope was emulsified in nutrient broth, and the bacterial content was estimated by comparison with standard opacity tubes. Colony counts of suitable dilutions on Bordet-Gengou plates were also made as a check on the approximate number of viable organisms.

Results.

The findings with the six samples of pooled normal human serum and the positive control serum "A.C.8" will be described first. The results are shown in Table I. It will be noticed that of the six samples of pooled normal human serum tested, two (batches 65A and CT.211) show a highly significant protective effect against a sublethal infecting dose of *Hæmophilus pertussis* in mice. Batch 77-1 also affords significant protection. The favourable results obtained with these three batches of serum are further demonstrated if they are compared with those of the reference standard serum "A.C.8".

One would expect that comparatively even results would be obtained with batches of pooled serum in which the serum of many donors was included. On the other hand, batches containing serum from a relatively small number of persons should be more likely to give divergent results. The figures shown in the second column of Table I tend to support this contention, although admittedly further data are required.

The figures on which the statistical significance is based are the actual number of mouse lungs infected or sterile in the different groups of test animals. Further reference to Table I indicates that if the degree of infection in the individual lungs is considered, the results are even more striking.

Confirmatory evidence of protective power was sought from another experiment carried out on the same lines as that just described, a different strain of *Hæmophilus pertussis* being used for the intranasal infection of the mice. The infecting strain "E.O." used in the first experiment was given in a dose of 50,000 organisms, as estimated by standard opacity tubes and confirmed by colony counts of suitable dilutions on Bordet-Gengou plates. In the second experiment, the data of which are shown in Table II, the infecting strain, "P58", was used in a dose of 5,000 organisms as judged by opacity tubes; but plate counts

TABLE I.

Protective Action of Pooled Normal Human Serum against Sub-lethal Infecting Dose of Hæmophilus pertussis *Given Intranasally in Mice.*[1]

Serum.	Number of Donors in Batch of Serum.	Dose of Serum. (Cubic Centimetres.)	Number of Mice in Group.	Intensity of Mouse Lung Infection.	Number of Mouse Lungs Specifically Infected.	Statistical Significance Compared with Untreated Control Mice.
N.H.S.[2] 65A	36	0·3	10	1, 0, 0, 0, 0, 0, 0, 0, 0, 0	1/10	$P^3 = 0·0005$
N.H.S. CT.211	10	0·3	10	3, 1, 0, 0, 0, 0, 0, 0, 0, 0	2/10	$P = 0·0028$
N.H.S. 77–1	133	0·3	10	4, 2, 1, 1, 0, 0, 0, 0, 0, 0	4/10	$P = 0·028$
N.H.S. CT.66A	16	0·3	10	3, 2, 2, 2, 1, 1, 0, 0, 0, 0	6/10	
N.H.S. 57C	27	0·3	10	4, 3, 3, 3, 2, 1, 0, 0, 0, 0	6/10	
N.H.S. C.T.212	10	0·3	10	4, 4, 3, 2, 2, 1, 1, 0, 0, 0	7/10	
"A.C.S"	—	0·25	10	3, 2, 1, 0, 0, 0, 0, 0, 0, 0	3/10	$P = 0·01$
Nil (controls)	—	Nil	10	4, 4, 2, 2, 2, 2, 1, 1 1, 0	9/10	

[1] Mice were given 50,000 *Hæmophilus pertussis* organisms (strain "E.O.") intranasally four hours after receiving serum, and were killed at the end of seven days, when cultures were made from the lungs.
[2] N.H.S. = Pooled normal human serum. "A.C.S." = Known potent adult contact serum (positive control).
[3] *P* = Probability factor. When *P* = 0·01 the odds are 1 in 100 that the result obtained is due to chance alone.

TABLE II.

Results of Further Protection Tests with Serum 65A.[1]

Serum.	Number of Mice in Group.	Intensity of Mouse Lung Infection.	Number of Mouse Lungs Specifically Infected.	Statistical Significance Compared with Untreated Control Mice.
N.H.S. 65A[2]	14	1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, C,[4] C	1/12	$P = 0·019$
N.R.S.[3]	15	4, 3, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0	5/15	
Nil (controls)	15	4, 4, 3, 2, 2, 1, 1, 0, 0, 0, 0, 0, 0, 0, C	7/14	

[1] Mice were given 5,000 *Hæmophilus pertussis* organisms (strain "P.58") intranasally four hours after receiving serum, and were killed at the end of seven days, when cultures were made from the lungs.
[2] N.H.S. = Pooled normal human serum. [3] N.R.S. = Normal rabbit serum. [4] C = Contaminated lung culture, result discarded.

showed that approximately only 2,000 viable *Hæmophilus pertussis* organisms were present. The smaller dose was chosen, as "P58" had given the impression that it possessed somewhat stronger invasive powers than "E.O." The serum selected for retesting, "65A", again affords significant protection, whilst normal rabbit serum does not.

When the results given by serum "65A" in each of the two experiments (Tables I and II) are combined, $P = 0·0002$. In other words, the odds against the results' being due to chance are 5,000 to 1. Other experiments were carried out to determine if better protection was afforded by the administration of the serum in divided instead of in single doses. The results have, so far, been inconclusive.

Discussion.

In addition to the experiments recorded above, there is clinical evidence to suggest the utility of normal human serum as a prophylactic agent against whooping cough. A considerable proportion of the healthy young adults from whom supplies of serum are obtained have previously had pertussis. It may be presumed that their serum contains protective antibodies in varying amounts, because if second attacks do occur they are usually very mild.[13] The favourable results reported by Cohen and Lapin[6] and Meader[14] were certainly obtained by the use of pooled serum from persons who had recovered from pertussis. However, animal experiments[10][11] indicate that convalescent serum varies greatly in its protective power. It is suggested, therefore, that clinically good results might be obtained if larger doses of normal human serum were used than the 10 cubic centimetres of convalescent serum given by Meader.

In the work recorded here the criterion of protection was the clearing of *Hæmophilus pertussis* from the mouse lung in seven days after an infecting dose of 5,000 to 50,000 organisms. The mouse is usually regarded as a somewhat insusceptible animal to pertussis. Experiments in these laboratories have shown, however, that six or seven days after an intranasal dose of approximately 50 living organisms, confluent growth on Bordet-Gengou medium may be recovered from the lung. Smaller doses have not been tried.

In the classical experiment of H. and E. J. Macdonald[12] the instillation of about 140 organisms into the nose and throat of two non-immunized children resulted in typical attacks of pertussis after a week's incubation. Two other children who had received a course of Sauer's vaccine remained well.

"Positive" cough plates, examined here, have rarely contained more *Hæmophilus pertussis* colonies than the number of organisms which, in the Macdonalds' experiment, produced whooping cough. Cough plates are exposed within six inches of a child's mouth and nose during a paroxysm of coughing.

If we reason on these lines, it seems improbable that an intimate contact would be exposed to infection by more than about 100 or so organisms at any one time. Further, in our hands passive protection has proved as effective as active immunization against intranasal infection in mice.

In the case, therefore, of an infant, the administration of a protective serum at the first possible moment after exposure and the immediate withdrawal from contact are indicated. If potent convalescent or "hyperimmune" serum is not available, pooled normal human serum seems worthy of a trial.

Conclusions.

1. Pooled normal human serum contains protective antibodies against *Hæmophilus pertussis* infection in mice.
2. Such serum may be of value as a prophylactic in young non-immunized children exposed to infection.

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A TRIAL OF "PROGYNON" THERAPY IN THYREOTOXICOSIS.

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WHILST confirming and extending the earlier observations of Lacassagne[2] on the production of mammary carcinoma in male mice, Cramer and Horning[1] reported the occurrence, after the prolonged application of œstrin to the skin of mice of both sexes, of changes extending beyond the sex organs, which had not previously been recognized. These consisted of the complete disappearance of fat with the development of emaciation, arrest of body growth, and pronounced changes in internal organs—extensive degeneration of the adrenal glands, production of a resting phase in the thyreoid gland, hypertrophy of the islets of Langerhans, and atrophy of the spleen and thymus. The general appearance was one of hypopituitarism bearing a striking resemblance to the clinical syndrome in man known as Simmonds's disease, and in point of fact the pituitary gland was as a rule strikingly affected. Of the first twelve pituitaries of their series examined by Cramer and Horning, three were adenomatous and eight enlarged macroscopically. The anterior lobe of the pituitary was mainly or solely affected. Enlargement of the pituitary after œstrin administration had previously been recorded by Korenchevsky and Dennison,[7] and Selye, Collip and Thomson.[11] Confirmation of the development of pituitary adenomata after prolonged œstrin administration was rapidly provided by McEuen, Selye and Collip[9] and by Zondek.[12]

In subsequent reports of more detailed microscopic examination of their material, Cramer and Horning[2][3] followed the progressive development of the pituitary changes described above by differentially staining the three types of pituitary cell. They concluded that the changes in the anterior lobe were an expression of an initial stimulation followed by exhaustion. Excessive amounts of circulating œstrin created a hormonal imbalance, which stimulated the chromophile cells of the anterior pituitary to secrete their specific hormones in an attempt to restore normal hormonal relationships, and led to increased functional activity of the anterior lobe of the pituitary, with accompanying hyperæmia and hyperplasia. Continued excess of circulating œstrin eventually exhausted the chromophile cells, which underwent progressive degranulation, became enlarged and assumed the appearance of chromophobe cells. The end result was an exhausted anterior lobe, greatly enlarged and congested, composed almost entirely of chromophobe cells. The cellular changes were the same whether eventual adenoma formation or merely anterior lobe enlargement resulted; this accounted for the condition of hypopituitarism produced by the prolonged administration of œstrin.

Deducing from their studies a physiological antagonism between œstrin and one or more of the hormones of the anterior pituitary lobe, Cramer and Horning[4] then proceeded to study on mixed strains of mice the effect of the simultaneous administration of purified preparations of the thyreotrophic hormone and of œstrin. They were successful in preventing the development of the characteristic changes in both the pituitary and mammary glands, thereby demonstrating the physiological antagonism between œstrin and the thyreotrophic hormone, as far as the pituitary and mammary changes were concerned. They suggested that thyreotrophic hormone might prove of use in the treatment of conditions alleged to be due to the unbalanced action of œstrogenic hormones.

Grumbrecht and Loeser[5] have made a careful and detailed study of the inter-relationships existing between the pituitary, ovary and thyreoid. The important conclusion they arrived at, from the point of view of the present communication, was that whereas follicular fluid itself administered parenterally to rats produced no thyreotrophic action, massive injections of œstradiol monobenzoate prepared from pregnant mares' urine ("Progynon-B-Oleosum") were capable of causing a temporary diminution in thyreoid activity, as proved by the histological picture of a resting gland and by the demonstrable diminution in oxygen consumption of the gland. The change in the direction of lessened activity was apparent after six days, reaching a maximum after fourteen days, and tended to pass off after eight or nine weeks. It was shown by quantitative biological assay that simultaneously there occurred a considerable diminution in the quantity of thyreotrophic hormone present in the pituitary gland. Their experiments led them to agree with the earlier similar conclusion of Heyl De Jongh and Kooy,[6] who were apparently the first to show that the resting phase of the thyreoid gland induced by œstrogenic hormones was not a direct effect, but an indirect one, produced by a depression of thyreotrophic hormone formation in the anterior lobe of the pituitary. On the basis of these findings, Grumbrecht and Loeser suggested that thyreotoxic manifestation of pituitary origin might be reduced by large doses of œstrin or œstradiol monobenzoate.

The experimental findings of both Cramer and Horning on the one hand and of Grumbrecht and Loeser on the other, supported and partly explained by the histological evidence of the one and the biochemical evidence of the other, led one to a reasonable hope that states of thyreotoxicosis of pituitary origin in man might respond to massive therapy with œstrogenic derivatives. In this investigation, therefore, an attempt has been made to discover whether clinical improvement could be produced in several cases of thyreotoxicosis by the use of large doses of "Progynon-B-Oleosum". The question of the role of the thyreotrophic hormone in thyreotoxicosis in man has been considered in a recent publication of mine,[10] and will not be further dealt with here; but it is desirable to mention that the rationale of the investigation inevitably presumes its importance as a primary ætiological factor in this disease.

Material and Methods.

The clinical material available consisted of the five cases of thyreotoxicosis already reported (Robinson[10]). After stabilization under the hospital régime (as before detailed) and withdrawal of the blood required for estimation of thyreotrophic and antithyreotrophic factor, each patient was given a course of intramuscular injections consisting of large doses of "Progynon-B-Oleosum Forte" (Schering, Limited).

A single dose for each patient was one ampoule of concentrated "Progynon-B-Oleosum" standardized to contain 50,000 international benzoate units (I.B.U.).

After each injection, each patient's clinical condition was closely studied, and both estimations of the basal metabolic rate and blood cholesterol determinations were continued twice or three times weekly as previously.

The frequency of repetition of the injections varied according to the response shown by the patient; but when

[1] This investigation was made during the tenure of the Marion Clare Reddall Scholarship and was generously aided by a grant from the National Health and Medical Research Council.

TABLE I.
Results of Treatment with Injections of "Progynon".

Number of Case and Type of Disorder.	Reference Case Number in Previous Article.	Stabilized Values.		Period of "Progynon" Injections.	Number of Injections of "Progynon" (each 50,000 I.B.U.[1]).	Progressive Evaluations following Injections. (Arrow Indicates Injection.)		Clinical Memoranda.
		Basal Metabolic Rate.	Blood Cholesterol Content. (Milligrammes *per Centum*.)			Basal Metabolic Rate.	Blood Cholesterol Content. (Milligrammes *per Centum*.)	
I. M.M. Toxic adenoma (secondary Graves's disease with nodular goitre).	II	+10% +4% +6% } +7%	137 154 147 } 146	2/5/39 to 18/5/39	4	←"Progynon" 1 ml. +23% ← +24% ← +19% +24% ← +20% +21%	145 142 — 131 113 82	Patient exhibited increased nervousness and restlessness. Slight increase in tachycardia.
II. C.T. Primary Graves's disease.	III	+37% +36% +38% } +37%	138 117 138 } 131	31/3/39 to 4/5/39	7	←"Progynon" 1 ml. +40% +34% ← +41% ← +47% +59% +29% ← +49% ← +39% ← +42%	122 132 141 101 130 117 151 145 134	Patient's general condition worse. Increased tachycardia, restlessness and irritability throughout period of injections. Developed furuncle of lip and stye of left eye corresponding to the time when the basal metabolic rate was 59%. Left hospital against advice.
III. M.W. Toxic adenoma (secondary Graves's disease with nodular goitre).	IV	+52% +51% +47% } +50%	106 130 133 } 123	23/3/39 to 26/4/39	6	←Venesection +38% +39% ←"Progynon" 1 ml. +23% +33% +29% ← +22% ← +12% 0% +13% ← +14% ← +15% +9% +5%	124 130 135 117 135 145 141 145 134 147 124 152 132	Patient showed consistent pronounced improvement from beginning of injection therapy. Nervousness subsided, hyperhydrosis disappeared, tremor diminished, palpitation and breathlessness vanished. Weight increased by seven pounds during course of treatment. One month after discharge from hospital patient was still gaining in weight and felt remarkably well.
IV. D.M. Primary Graves's disease.	V	+22% +24% 19% +18% } +21%	150 134 148 138 } 143	23/3/39 to 18/4/39	5	←"Progynon" 1 ml. +26% +25% +28% +28% ← +28% ← +26% ← +10% ← +22%	140 132 129 128 160 112 128 130	Patient's condition unchanged throughout injection period.

[1] International benzoate units.

TABLE I.—*Continued.*

Results of Treatment with Injections of "Progynon".—Continued.

Number of Case and Type of Disorder.	Reference Case Number in Previous Article.	Stabilized Values.		Period of "Progynon" Injections.	Number of Injections of "Progynon" (each 50,000 I.B.U.[1]).	Progressive Evaluations following Injections. (Arrow Indicates Injection.)		Clinical Memoranda.
		Basal Metabolic Rate.	Blood Cholesterol Content. (Milligrammes *per Centum.*)			Basal Metabolic Rate.	Blood Cholesterol Content. (Milligrammes *per Centum.*)	
V. D.M.						←"Progynon" 1 ml.		
Primary Graves's disease.	VII	+5% +3% } +4%	154 166 } 160	3/5/39 to 20/5/39	5	−2%← +7%	157 171	Patient's condition unchanged during injection period.
						←		
						+1%	172	
						−2%	180	
						←		
						+9%	170	
						←		
						+5%	178	
						+4%	181	
						−2%	177	

[1] International benzoate units.

no improvement was demonstrable, one ampoule containing 50,000 I.B.U. was given twice a week. The total course prescribed varied from four to seven injections, extending over a period of three to five weeks.

Results.

The results are shown in Table I. Clinical histories of the patients have already been published in this journal.

It will be noticed that only one of the patients examined (Case III) showed improvement with the "Progynon" therapy, though in this case the improvement was striking and maintained. Of the others, two seemed to show a definite exacerbation of their symptoms (Cases I and II), as evidenced by their clinical appearance and the quantitative evaluations of the basal metabolic rate. The remaining two patients exhibited no change at all (Cases IV and V).

Discussion.

The results indicate that the clinical application of the experimental work upon which this investigation was founded, is unjustified. As would be expected in view of the absence of significant clinical improvement, the blood cholesterol values were uniformly unaffected by the treatment.

With regard to the single case in which the "Progynon" therapy did seem to be of definite value, the possibility exists that the improvement was simply a spontaneous remission of the disease, though this seems unlikely in view of the type of thyreotoxicosis concerned, and of the fact that improvement occurred immediately after the commencement of "Progynon" therapy. A more probable explanation is that, as the thyreotoxic condition was definitely related to the menopause in this case, the hyperthyreoidism was an expression of a hormone imbalance induced by the general endocrine disturbance of this period, and that this imbalance was corrected by the therapy adopted. In the treatment of cases of this nature, therefore, œstrogenic hormone therapy may have a definite value, but its mode of action then consists possibly in the readjustment of a normally functioning pituitary to a reduced functional level, rather than in the adjustment to normal of an overacting gland.

It is difficult to understand the exacerbation of the clinical states induced by the treatment in two of the cases, in view of the known experimental facts. It is well to recall, however, that of these two patients one was an elderly woman long past the menopause and the other had suffered an artificial menopause ten years previously. It would seem that the complete absence of the ovarian stimulus from the pituitary over a long period induces in the latter an abnormal sensitivity to the action of œstrogenic hormone, so that the experimental work done may merely have served to produce in the pituitary the initial phase of stimulation described by Cramer and Horning as the first stage in the response to administration of œstrin. The remaining two younger patients, whose ages made them rather more comparable to the laboratory animals mentioned, were certainly not influenced in the same way.

The results suggest that a more extensive trial of the effects of "Progynon" therapy in menopausal thyreotoxicosis is desirable, since it is impossible to draw conclusions as to the beneficial effects of this type of treatment on the basis of the single case studied here.

It is interesting to remark, too, upon a discrepancy in the results of the experimental workers mentioned. Grumbrecht and Loeser described the changes in the thyreoid gland of rats indirectly induced by œstrogenic hormone administration, as being temporary and tending to pass off within eight or nine weeks. The histological changes described in the pituitary following the prolonged administration of œstrin in mice by Cramer and Horning—namely, increased chromophobe cell formation and hæmorrhagic chromophobe adenomata—must surely represent a permanent and not a reversible change. Admittedly, the animals, the type of œstrogenic preparation, and the method of administration used were different in the two series of experiments; but one would have expected the qualitative structural and functional changes induced in the thyreoid gland to be the same, if the mechanism of

production were identical in each case, as the close agreement in other features of the two experiments seemed to indicate. Further experimental studies are required to elucidate this point.

Summary.

1. On the basis of experimental work and suggestions arising from it, an attempt has been made to treat human patients suffering from thyreotoxicosis by massive doses of œstrogenic hormone ("Progynon-B-Oleosum").

2. Success has not been achieved in this effort, with the exception of one case of thyreotoxicosis occurring soon after the menopause.

3. The interpretation of the results is discussed.

Acknowledgements.

I desire to thank the Board of the Royal Prince Alfred Hospital and Professor C. G. Lambie once again for permission to investigate the cases; Miss L. E. A. Wright, B.Sc., for the cholesterol assays; and Mr. W. S. Stephen for assistance with the basal metabolic rate determinations.

I wish also to thank Professor C. G. Lambie and Dr. V. M. Trikojus for advice and criticism during the work.

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Reports of Cases.

RUDIMENTARY CERVIX NECESSITATING CÆSAREAN SECTION.

By ELLEN M. KENT HUGHES, M.B., B.S.,
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MRS. C.C., aged twenty-nine years, on December 22, 1939, complained of sterility and dysmenorrhœa. She had a small anteflexed uterus and a minute cervix. She was given theelol, 2,000 international units (one capsule) three times a day, and on February 24, 1940, the uterus had enlarged to the size of a six weeks pregnancy. The condition of the cervix was not noted.

The pregnancy progressed normally, and on October 15, 1940, labour pains commenced. On examination the fœtal head was well down, but no cervix could be felt. The contractions during the next forty-eight hours gradually increased in severity, but as no cervix could be felt the patient was given a general anæsthetic. Then it was found that the os was represented by an aperture which would just admit a number 12 knitting needle, and the contractions were so severe that it seemed as if the lower uterine segment, which was tightly stretched over the infant's head, might rupture.

Accordingly a Cæsarean section was performed after the aperture had been dilated with metal dilators, and a rubber catheter was tied in for drainage. The child was alive and weighed six pounds. Both mother and child progressed normally. An intrauterine douche was given every second day after the catheter was removed.

Two months after the delivery the uterus had involuted normally, but the cervix was represented only by a dimple in the centre of a rosette of tissue, just discernible to the finger tips.

As several medical men could find no reference to this condition in standard works on obstetrics, I thought that the case was of sufficient interest to warrant a report.

RUPTURED SPLEEN.

By THOMAS F. ROSE, M.B., B.S. (Sydney),
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Clinical Record.

THE patient, a girl, aged seven years, was admitted to the East Ham Memorial Hospital with the following history, obtained mostly from her mother. Twenty-eight hours prior to her admission to hospital, whilst running on the footpath, the child fell on the edge of the gutter and struck her chest on the kerb-side. She could not state which side of the chest was injured and said that she was "winded" but not actually hurt. After finishing her game she walked home, had tea and went to bed. Six hours after the accident she complained of severe generalized abdominal pain, later radiating to the right iliac fossa. Her mother also noticed that she had become very pale. However, the pain abated after a few hours and she went to sleep. Next morning, about twenty-four hours after the accident, she walked one mile to see her doctor, who diagnosed an "acute abdomen". The patient was then allowed to walk a further mile to the hospital, where she was immediately admitted.

There was no history of shoulder pain and there were no other symptoms.

On her admission to hospital the child was seen to be very pale and slightly breathless, with a pulse rate of 110 beats to the minute. The temperature was normal. Her only complaint at that time was one of pain localized to the right iliac fossa. The abdomen was a little distended, and slight generalized tenderness and rigidity were present, except in the right iliac fossa, where the abdomen was very tender and of board-like rigidity. No tenderness was present posteriorly. Rectal examination revealed no abnormality. The heart and lungs were normal. There was no superficial bruising or evidence of fractured ribs. The urine was normal.

The intense pallor and abdominal signs showed that intra-abdominal hæmorrhage was present; but these signs were too equivocal to allow of an exact diagnosis as to its origin.

Accordingly an immediate exploration of the abdomen was performed under general nitrous oxide and oxygen anæsthesia. At the same time a blood transfusion of stored group "O" blood was administered by the "continuous drip" method. The abdomen was entered by a right paraumbilical incision. Blood and clots gushed forth immediately the peritoneum was incised. Exploration revealed a mass of blood clot lateral to the caecum in the right iliac fossa. There was also blood throughout the abdominal cavity, a pint being sucked away. The source of the bleeding was found to be in the spleen. This was completely bisected by a jagged transverse tear running into the hilum. The hilar vessels were not involved in the tear, and both segments of the spleen received an adequate blood supply from the branches of the splenic artery. Both cut surfaces were bleeding freely. Splenectomy was easily performed after the abdominal incision had been prolonged slightly proximally. An inspection of the diaphragm as far as was possible revealed no bruising. The abdomen was then quickly closed, residual blood being left inside. The transfusion was carried on and the child made an uneventful recovery. A blood count made about four days later revealed 3,500,000 red cells per cubic millimetre and a hæmoglobin value of 60%. Iron was administered and the blood picture returned to normal in about one month.

The spleen appeared to be normal, and histological examination revealed no evidence of any abnormal structure.

Discussion.

This case is reported because it presents several interesting features.

1. Though the spleen appeared to be normal both macroscopically and microscopically, yet it ruptured from what seemed to be a trivial accident, which did not even damage the parietes. Further, this trivial accident caused complete bisection of the spleen.
2. Though the spleen was completely bisected, no symptoms of bleeding appeared until six hours after the accident.
3. Though the abdomen was full of blood, the child was able to walk about and walked two miles to hospital without apparent difficulty, except for some breathlessness.
4. The main symptoms and signs were localized to the right iliac fossa, although they began with generalized abdominal pain and were the symptoms and signs of acute appendicitis. Observation of the extreme pallor and slight breathlessness, however, confirmed the diagnosis of internal hæmorrhage.
5. The spleen was easily removed through a right paramedian incision.

AGRANULOCYTOSIS AND HEPATITIS FOLLOWING SULPHAPYRIDINE TREATMENT.

By ALAN FINGER,
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Clinical Record.

F.J.A., A MAN, aged twenty-nine years, was sent to the Metropolitan Infectious Diseases Hospital, Northfield, on March 26, 1941, with the provisional diagnosis of meningitis. The history, sent with the patient, was one of urethritis, not proved but presumed to be gonococcal, treated with "about 60 tablets of 'M & B 693'" over the period of ten days which ended on March 20. On March 25 the patient was seized with colicky abdominal pains which lasted for two hours. The next day his neck was stiff and he was febrile. The man himself said he had had a sore throat for some days and that it was growing worse.

On his admission to hospital he was obviously very ill; his temperature was 101·8° F., his pulse rate was 136 per minute and the respirations numbered 28 per minute; swollen, tender glands and periglandular tissues were noted in the neck anteriorly, his mouth and tongue were dirty, though no obvious lesions were present, and his breath was foul. His throat could not be properly examined on account of pain. No abnormality was detected in his chest. Neither spleen nor liver was palpable. There was no apparent urethral discharge and no prostatic tenderness. His neck was stiff from the painful angina. No abnormal constituents were found in the cerebro-spinal fluid.

Blood examination shortly after his admission to hospital revealed that the erythrocytes numbered 4,100,000 and the leucocytes 1,000 per cubic millimetre. Only lymphocytes and mononuclear cells were seen on a smear.

The diagnosis of agranulocytosis was thus confirmed. The patient was given five ampoules of "Pentnucleotide" per day and symptomatic treatment. Next day his condition was much the same, but he had greater difficulty in swallowing, his conjunctivæ and skin were jaundiced and he was tender over the liver, which was not palpable. He had some increased breath sounds at the base of the left lung. A blood count revealed that the erythrocytes numbered 3,700,000 and the leucocytes 900 per cubic millimetre.

The next day he was much worse; he was unable to swallow and was more jaundiced; his temperature was 104° F. and the respirations numbered 40 per minute. A blood count revealed that the erythrocytes numbered 3,400,000 and the leucocytes 1,600 per cubic millimetre. In a smear a few neutrophile cells and some primitive granular cells as well as mononuclear leucocytes and lymphocytes were seen.

On March 29 his condition was much worse. He was irrational and very jaundiced, and coughed up large quantities of foul purulent material. He had signs of extensive pneumonia. At 2 p.m. a blood count revealed 3,800,000 erythrocytes and 7,500 leucocytes per cubic millimetre. In a smear large numbers of primitive granular cells were seen.

The patient died early next morning. At the post-mortem examination purulent tracheo-bronchitis and broncho-pneumonia involving most of the lung tissue were found. There was about three ounces of yellow pericardial fluid, and the right side of the heart was enlarged. The liver weighed 80 ounces and gross toxic changes were present in it. The spleen was slightly enlarged and very friable.

Comment.

The features of the case which make it noteworthy are the rapidity of onset of the agranulocytosis (the condition was well developed within two and a half weeks of commencement of sulphapyridine treatment), the granulocytosis that followed the administration of "Pentnucleotide", the advance of the septic condition despite this granulocytosis, and the gross hepatitis.

Reviews.

CEREBRO-SPINAL FEVER.

A KNOWLEDGE of the epidemiology of cerebro-spinal fever, or a perusal of the article by Lieutenant-Colonel Holmes in this journal on May 3 reveals that the occurrence of an epidemic of this disease in Australia during or at the end of the oncoming winter is a real possibility. The wise practitioner will therefore revise his knowledge of the disease before that time comes. For such a purpose he need go no further than a recent short survey entitled "Cerebro-spinal Fever", by Denis Brinton, a prominent English neurologist.[1] It became plain to Brinton early in the vast English epidemic of 1940 that the disease would probably continue its ravages until the end of the war, and it was therefore essential that practitioners should be thoroughly acquainted with its characters, course and treatment. The book he has written is designed for this single purpose and fulfils it admirably. It is brief, pleasant to read, adequate for its purpose and intensely practical. There is nothing in it that is devoid of interest, and little indeed devoid of practical value. Those whose time is so urgently filled that they cannot read 150 pages of large type can easily and rapidly pick out the parts they particularly need, for the slim volume is divided into clear and logical sections.

Epidemiology and ætiology are quickly disposed of, and the essentials of prophylaxis under civil and service conditions are outlined. Bacteriology and pathology are given just enough space to make plain what underlies the clinical picture of the disease. The clinical course and its variants as seen before the days of sulphonamide therapy are thoroughly discussed. One must commend the simplicity of Brinton's description. He has wisely discarded the many types of the disease sometimes described, which in fact are but slight variations of what he calls the "ordinary form". The symptoms, signs, possible complications and sequelæ are clearly described. Certain variants of the disease which account for only 10% of all the patients affected he thinks deserve separate brief description. They are the fulminating, abortive and chronic septicæmic forms and posterior basic meningitis of infants. Criteria of diagnosis, with cerebro-spinal fluid changes, and differential diagnosis rapidly follow.

Brinton then discusses treatment. Sulphonamide chemotherapy rightly receives more space than any other subject, for properly used it has very greatly reduced the mortality, duration, severity and sequelæ of a very grave disease. The drugs of choice, immediate and maintenance dosage, modes of administration and toxic effects are thoroughly described without waste of words. Brinton knows what he has found to be effective and says so plainly. Many physicians prefer to use a bigger initial dose than he does; but he has had experience enough to be satisfied, and the purpose of his book is better served by a single emphatic recommendation than by suggested alternatives. On one point he must be criticized. It is the omission of alkalis in the treatment of sulphonamide hæmaturia. They are just as important as the fluids he recommends. It is good, however, to see in a British publication the more scientific terms sulphapyridine and sulphathiazole replacing the clumsy trade names that have held sway for too long. Serum therapy and lumbar puncture are briefly dismissed, for the former is being abandoned as no longer necessary and the latter is used only for diagnosis and then for relief of headache and restlessness.

This little book deserves nothing but praise and the strongest recommendation. No subject could be more important at present to the civilian as well as to the service doctor. The book is thorough enough to serve all his practical needs, short enough to demand no more of his time than the subject deserves, and interesting enough to hold him throughout. It should be read by all Australian doctors before this winter is much further advanced.

[1] "Cerebrospinal Fever", by D. Brinton, D.M., F.R.C.P.; 1941. Edinburgh: E. and S. Livingstone. Demy 8vo, pp. 170, with four photographs. Price: 8s. 6d. net.

The Medical Journal of Australia

SATURDAY, JUNE 21, 1941.

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HOSPITALS AND THEIR EXECUTIVE OFFICERS.

If the average person were asked to define a hospital, he would probably say that it was an institution to which the sick could go for treatment. This definition would be accepted, for the treatment of the sick is the chief function of the modern hospital. But most people know that hospitals have other functions. They are places at which nurses are trained to care for the sick, and they are also places where disease is studied. Here medical students are trained in the recognition and treatment of disease, they are trained in the treatment of patients as sick men and women, and they are taught to place the welfare of the patient before all other considerations. Moreover, at hospitals medical men and women after graduation perfect their knowledge and make themselves proficient in the technical side of their profession. Beneath a hospital roof patients, doctors, nurses and other attendants have to live; food costs money and so do drugs, dressings and equipment of all kinds, to say nothing of the upkeep of buildings and so forth. The hospital is thus an enormous business concern and its control is far from simple. It is usual to speak of the medical and business sides of hospital administration, and in most Australian hospitals dual control has been adopted—the medical side is administered by a medical superintendent and the business side by a non-medical business manager or secretary. Sometimes this arrangement has been satisfactory because of admirable qualities displayed by the heads of the two departments. This is not always the case, and for reasons which need not be discussed at present. When dual control works smoothly it is regarded by most people as satisfactory; but there are many who hold that the interest of the hospital is best served if it has one administrative head—the chief executive officer. Certainly, if there is only one head the main cause of trouble in hospital administration is eliminated.

In November, 1939, when the report of the magisterial inquiry into the affairs of the Royal North Shore Hospital of Sydney was published in this journal, opportunity was taken to discuss the administration of hospitals. Reference was made to an article by Sir Robert Wade, published in *The Australian and New Zealand Journal of Surgery*. Sir Robert Wade, who is peculiarly qualified to express an opinion on such matters, suggested that a medical man should be trained for the position of chief executive officer and that the subjects of his training, in addition to the administration of a hospital on the medical side, should include business methods and organization, secretarial duties and all things necessary to the equipment of a hospital manager or secretary. In other words, as we explained on that occasion, a chief executive officer of the type advocated would have to undergo a long apprenticeship and would have to qualify in two spheres, medicine and commerce. We insisted that it was not a question of taking a medical graduate and thrusting him into a business position—he would have to study business methods and attain some proficiency in them. It was also pointed out that there would have to be an organization or body which could give a medical man his *cachet* in business training. Lest it be thought that the possibility is forgotten, we would repeat that a business man, a hospital secretary, could, if he wished, study medicine, graduate, go through a course of training as a resident medical officer in hospitals and become a chief executive officer.

Reference to this matter has again become necessary for two reasons. The first of these will be found in some strongly expressed opinions in the report of the Parliamentary Committee into Hospital Administration and Staffing in New South Wales, published *in extenso* in the issue of April 19, 1941. The committee expressed the opinion that the administrative side of medicine should be regarded as one of its specialties and that provision should be made in some way for the training of graduates so that some of them might specialize in hospital administration. The committee also declared that if a medical officer possessed practical knowledge in medicine and in addition a sound knowledge of hospital administration and business management, he should undoubtedly have first claim to be appointed to the "combined position of medical superintendent and chief executive officer". (We have used the term chief executive officer as including these two positions.) Following on the appearance of this report the Council of the New South Wales Branch of the British Medical Association decided to ask the New South Wales Post-Graduate Committee in Medicine to institute a course for the training of chief executive officers of hospitals. This is the second reason for our reference to the subject. The New South Wales Branch Council has set the Post-Graduate Committee a peculiarly difficult task; but it is to be hoped that something will come of the suggestion. Even if the post-graduate body decides that the present is an inopportune time to institute such a course, it will, we trust, make complete plans for the inception of a course at a later date. It may be useful to remember that if such a course of study is compressed into a relatively short time, practitioners from other States may be persuaded to enrol as members. After this war is over there will in all probability be increased opportunities for medical graduates to specialize in hospital administration. Further, if any plans are made, it will most likely be decided to enlist the aid of hospitals

already controlled by a single medical chief executive officer. Something in the nature of an apprenticeship system will be required, and it is difficult to imagine that any hospital that has achieved the blessing and comfort of ideal control would be unwilling to aid in an extension of the system to others.

Current Comment.

FOOD ALLERGY.

AN association between attacks of eczema and the consumption of certain foods has been long recognized, but research on food allergy entered upon a vigorous phase of activity when Richet and his collaborators published a work on alimentary anaphylaxis in 1919 and again when Vaughan in 1927 announced that certain types of migrane are of an allergic nature. Just ten years ago the subject attained the dignity of a book all to itself.[1] As is usually the case, many advocates of the new doctrine allowed their enthusiasm to get the better of their judgement, and claims were made for allergy which were extreme, whilst other factors especially nervous and psychic were neglected. However, at present a more critical approach is in use and a more logical attitude adopted.

As is well known, the simplest allergic phenomena are the contact reactions in which a dermatitis or other local disturbance arises from contact with the food allergen. The number of foodstuffs which produce skin reaction in sensitive persons handling them during packing, manufacturing or cooking is certainly great. It is somewhat amusing to note that the latest foodstuff to be added to the list is the carrot, the production and consumption of which have recently been vigorously advocated in Britain.[2] In this investigation H. R. Vickers reported that some 17% of the girls in a cannery were sensitive to the carrot and had a genuine dread of the carrot rash from which they suffered, unless the handling was reduced to a minimum and protective rubber gloves were worn. We may legitimately include in this category most of the allergic disturbances of the alimentary canal, from the blisters on the lips, or "canker sores" in American phraseology, also stomatitis, to the often serious derangements of the colon.

The second type of disorders classifiable under food allergy are those consequent upon the transport of the ingested allergen to the tissues of the body by the blood stream. We may omit inhalation cases, those, for example, which arise when flour gains entry to the circulation through the lungs of sensitive millers, bakers and cooks. Spasm of smooth muscle giving asthma or actually simulating calculus in the bile ducts or ureter, urticaria, angioneurotic œdema, leucopenia, rhinitis, eczema, headache and migraine are amongst the many now familiar phenomena which minute amounts of the exciting substance can evoke. The rate at which ingested allergen can arrive at the periphery from the alimentary canal has been determined by the simple device of injecting serum from a sensitive subject under the skin of a non-reacting person, thus producing a small patch of specifically sensitive tissue. The appropriate food is eaten and the time noted when the injected region visibly responds.[3]

Perhaps the most puzzling feature in food allergy is the entry of the allergen into the blood stream from the alimentary canal and also its penetration of the skin, for the exciting substance is unquestionably a protein. Many persons sensitive to underdone beef can eat fully cooked flesh with impunity; many who react violently to raw milk have no trouble with milk powder—here it is the lactalbumin which is operative. Cases have been reported in which egg-sensitive persons were free from all bad effects if the ingested eggs were hard boiled.[1] Physiology tells us that protein to be absorbed must be broken down into amino-acids which are assimilated as such; but here in allergy there is evidence that unaltered protein, foreign to the body, can be found in the blood stream some twenty minutes after oral feeding. The suggestion was once put forward that minute portions of protein, sufficient, however, to evoke the reaction, are seized upon by white cells and carried through the wall of the villus into the central lacteal. But the rectal administration of the food allergen brings about as quick a response as feeding with a duodenal tube[2] and then, more remarkable still, equally quick absorption of the food allergen has been shown to occur from the vagina and cervix,[3] the pleural, peritoneal and pericardial cavities. How a protein like the lactalbumin of cheese can penetrate the cuticle and produce a dermatitis is a mystery, but the fact is indisputable.[4] One thinks of the sweat and sebaceous ducts as the most likely portals, but the difficulties in picturing the precise method of penetration are still formidable. Apparently no matter how great the molecular weight and volume and consequently slow the rate of diffusion, any protein foreign to the body may produce dermatitis when applied to the skin of a person sensitive to that protein. Natural selection operating throughout human and even pre-human history must have eliminated many of those prone to food allergy of a serious gravity; the marvel is, however, that so much remains. One comment of a psychological character may be added in conclusion. Few memories are so tenacious and so vivid as those of gastro-intestinal irritation following the ingestion of a particular food; often that foodstuff is struck out of the diet and is never wittingly consumed again. But if the allergic effects are dermal, pulmonary or nasal no such association is elaborated in the mind and the disturbing reaction may be repeated indefinitely.

[1] Rowe: "Food Allergy", 1931.
[2] *The British Journal of Dermatology and Syphilis*, February, 1941.
[3] M. Walzer: "Studies in Absorption of Undigested Proteins in Human Beings; Simple Direct Method of Studying Absorption of Undigested Protein", *The Journal of Immunology*, Volume XIV, 1927, page 143.

PSYCHIC FACTORS IN DYSPEPSIA.

AN interesting article on "personality disorders" causing digestive complaints appears in the March, 1941, issue of *The Bulletin of the Johns Hopkins Hospital* under the name of Dr. G. Canby Robinson. The theme is by no means new, but it is good to have this eminently sane and useful presentation of the problem. Sullivan in 1938 found "personality factors" operative in 70% of 200 patients whilst eight years earlier Stevenson had discovered the same provocative agent in 75% of 150 patients admitted to the gastro-intestinal division of the Cornell Clinic in New York. The term "nervous indigestion" and what it connotes have been before the profession for a considerable time, well over half a century; but there is a danger today that with the perfection of diagnostic procedures, chemical and physical, the role of mental states may be overlooked in an examination of the stomach. That such functional dyspepsias may pass over into organic disorders is now a widely held belief. Warnings have again and again been issued to general practitioners by leaders in the profession that a persistent dyspepsia should arouse suspicion of cancer and that a careful examination of the patient should always be made with this in mind. This is perfectly sound advice so long as the patient's fears are not unnecessarily aroused; but those who stress the ulcerous and possibly malignant nature of dyspepsias which do not respond to diet and simple medication should remember that the biographies of many distinguished men present us with evidence to the contrary. Thomas Carlyle suffered as a young man from gastric pain which

[1] J. H. Tresher: "Limitations of Food Allergy", *The Medical Clinics of North America*, Volume XXV, March, 1941, page 529.
[2] I. Gray and M. Walzer: "Studies in Absorption of Undigested Protein in Human Beings; Absorption following Oral, Duodenal and Rectal Administration", *Journal of Allergy*, Volume XI, March, 1940, page 245.
[3] M. Rosensweig and M. Walzer: "The Absorption of Antigen from the Vagina and Cervix in Humans", *Journal of Allergy*, Volume IX, 1938, page 395.
[4] A. Walzer: "The Absorption of Protein through the Skin", *Journal of Allergy*, Volume X, 1938, page 68.

he described as a rat gnawing at his stomach. This dyspepsia dogged him throughout his subsequent career; but the fact remains that he died at the age of eighty-six and retained considerable physical and mental vigour to the end. His contemporary, Thomas De Quincey, despite chronic dyspepsia on the top of opium addiction, lived to the age of seventy-four.

The knowledge that mental states influence the activities of the large intestine is as old as humanity, and indeed the bowels became symbolic of certain emotional states, and the frequent use of the term by Puritan writers sounds today crude and incongruous. But the stomach was not admitted into the exalted region of metaphor, and even today gastric participation in excited feelings is not usually brought under review. Nevertheless nothing is more certain than that fear, anxiety, frustration, worry, fatigue or even general emotional instability can profoundly affect the stomach. After all, the alimentary canal is one and indivisible; there are no bulkheads separating compartment from compartment; if one level is affected, then those above and below share in the discomfiture, as is evidenced by one of the oldest diagnostic signs, alas still unexplained, the furred tongue arising from inflation of the colon and other intestinal aberrancies. In Britain it has long been known that escape from the cold and gloomy winter to Mediterranean sunshine warded off dyspeptic attacks. We may further assert with assurance that under war conditions, no matter how excellent the selection, cooking and distribution of food may be, dyspepsia will assail a large number of soldiers who in civil life were free from this affliction. Recent medical literature has let us know how prevalent digestive disorders are in bombed cities; no doubt the irregular times of feeding, the limited choice and the defective cooking play their part here but the nervous factor remains.

What is the cause of gastric pain and faulty digestion in these unhappy emotional states? When Pavlov discovered the psychic or preparatory flow of gastric juice it was thought that here was the key to the problem. Certainly if eating is not accompanied by pleasure and still more so if pain is associated with the act, as occurs with, say, an alveolar abscess, digestion is seriously embarrassed. The reception of bad news makes the food, in layman's phraseology, "lie like lead in the stomach". If Professor Carlson's unnamed successor to Alexis St. Martin did not show just the same secretory activity in anticipation of a meal which Pavlov's dogs displayed, he unquestionably manifested improved digestion when the act of eating was pleasurable. The psychic flow of juice can explain much but not the severer forms of painful dyspepsia of mental origin, the rat gnawing at the stomach. A suggestion was put forward a few years ago that as pain and pleasure are thalamic, the hypothalamus, acting through the pituitary, can control the secretion of the thick glairy mucus that lines the gastric mucous membrane. That this mucous coat is of considerable functional importance was shown by Beaumont over a hundred years ago, but its significance was lost sight of until the recent development of gastroscopic methods. Something yet has to be learned. If Alvarez's axiom is correct that disorders of digestion are disorders of motility, we must seek a psychic influence operating on the complex movements of the stomach, the surface ripples and postural contraction of the cardiac end, the "pyloric mill" and the selective opening and closing of the gastro-duodenal sphincter.

In his article in *The Bulletin of the Johns Hopkins Hospital*, Robinson makes a recommendation of direct interest to the practising physician. Dyspepsias arising from "personality disorders", such as domestic unhappiness, including marital friction, anxiety, worry, hypochondria (and the derivation of this word is interesting) are in most instances to be treated not by the psychotherapist but by the general practitioner who is familiar with the home environment and the general history of the patient's family. Naturally ordinary therapeutic measures are to be taken, but the family physician is best able to win the patient's confidence and bring about a healthier mental outlook and with this a more normal functioning of the stomach.

LEPTOSPIROSIS.

THROUGHOUT the last century there have been reported in Europe a number of epidemics of a disease characterized by jaundice and fever, but it was not till 1886 that Adolph Weil established it as a clinical entity. To it his name was later given. Almost thirty years passed before the causal agent was identified as a coarsely spiral micro-organism, so distinct in its morphology that Noguchi erected for it a new genus, the *Leptospira*. The particular organism was named the *Leptospira icterohæmorrhagiæ*. Since that time information has gradually accumulated and a number of other members of the group *Leptospira*, very similar in their morphology but differing in their serology and pathogenicity to man, have been described. They are world-wide in distribution, and are usually associated with rats, but sometimes with dogs, foxes and ferrets. The organisms are passed in the urine of the infected animals, and so contaminate stagnant streams and swimming pools, swamps, sewers, mines and other damp rat-infested places, and thus reach human beings. They enter the body through the mouth or through skin that is soggy or broken.

The *Leptospira* is the cause of a number of diseases in man. In 1934 in this journal C. G. Morrissey and later J. T. P. Cotter and W. C. Sawers described an epidemic of Weil's disease occurring in Queensland cane-cutters during 1933 and followed by a number of sporadic cases. On March 19, 1938, we described in these pages some of the clinical features of Weil's disease, and particularly the role of rats in its causation. On March 29 of this year J. O. Poynton included the leptospiroses in a list of diseases to which our troops may become exposed by wading in swamps or swimming in stagnant pools. The other diseases attributed to these organisms are Japanese "seven-day fever" and a syndrome known in different parts of Europe and Asia as "field fever", "summer influenza", "harvest fever", "swamp fever", and so on. These leptospiroses have now been reported from five continents, in places of widely differing climate, and the distribution of the organism is probably as widespread as that of civilized man. Where men go, rats go, and where rats go there goes *Leptospira*. The classical case of Weil's disease is characterized by a sudden onset with rigors, fever, headache, prostration and muscle pains, and in a few days by deep jaundice, hæmaturia and hæmorrhages in skin and from mucous surfaces. It is now becoming plain, however, that many milder cases occur in which jaundice is quite absent. Indeed it seems probable that these outnumber those in which jaundice is present. There is, moreover, little difference between these and the variety of other fevers attributed to the *Leptospira*.

A small outbreak of Weil's disease recently reported by W. P. Havens, C. J. Bucher and H. A. Reimann[1] demonstrates admirably the risk of infection from unsuspected sources and the clinical variations of the disease. Seven young men swam in a public bathing pool formed by a dam in a creek near Philadelphia. Near by were barns and refuse pits infested by rats. From four to twelve days after swimming each of the young men became ill and feverish. Two were gravely ill with jaundice and hæmaturia, following a period of fever, malaise, anorexia, headache and pains in the back and limbs. Hospital care was necessary and one man died. The others suffered for a few days from the same premonitory complaints, but did not develop jaundice or hæmaturia. Two were obliged to spend some days in bed, the other three remained ambulatory. The clinical picture of these milder cases is not unlike that of many examples of the other leptospiroses, and the diseases can be regarded as being as closely related as are their causal organisms. *Leptospira* occurs in Australia, just how extensively is not known. Fortunately man seldom comes in contact with the excreta of infected rats, and so the disease seldom occurs. It is well, however, that the possibilities of infection should be recognized, and for the now unquestioned fact to be known that jaundice is not a *sine qua non* of the diagnosis.

[1] *The Journal of the American Medical Association*, January 25, 1941.

Abstracts from Medical Literature.

OPHTHALMOLOGY.

The End Result of Tuberculous Uveitis.

G. STROMBURG (*Klinische Monatsblätter für Augenheilkunde*, April, 1940) made a survey of 500 patients with uveitis of tuberculous origin who had been treated at Axenfeld's clinic in Freiburg between 1900 and 1930. One hundred and seventy were available for reexamination, 124 having died and 176 having moved in the meantime. Only 44 of those reexamined were males. Ninety-seven patients had been observed for at least twenty years. In 95% the disease was originally, or had become, bilateral. The period of greatest incidence was between the second and third decades. With men the curve declined uniformly after that period, but in women it remained high and rose further during the climacteric. After parturition the incidence increased. Only 25% retained full visual powers, and 40% were blind or almost blind in both eyes. At least half of these were blind before the age of forty. Secondary glaucoma was the main cause of blindness. Operation, especially the broad iridectomy in 83 cases and transfixion in 23, had reduced tension permanently in only 30%. The author reaffirms the conclusion that a tuberculous attack successfully overcome in youth does not give protection from a later intraocular lesion; in fact he considers that a predisposition may even be developed. An insidious form of cyclitis, particularly in women, appears to have a very relentless nature. The prognosis of complicated cataract is much more favourable. Of 37 practically blind eyes, nine recovered useful sight, 11 did not, and in 17 phthisis developed after operation. The author concluded that intraocular tuberculosis is one of the chief causes of blindness amongst strong men in the most productive years of life.

Splanchnectomy in Malignant Hypertension.

TOOKE AND NICHOLLS (*The British Journal of Ophthalmology*, March, 1941) reported fifteen cases of malignant hypertension in which treatment by supradiaphragmatic splanchnectomy was adopted. From every standpoint, including that of the *fundus oculi*, two patients were cured, the condition of three was markedly improved, that of eight was moderately improved, and the condition of one was unchanged. However, the improvement in the *fundus oculi* was the most dramatic. The changes, as they were recorded for the better, simply reflected the general lowering of the blood pressure and the improvement in the findings on the chemical examination of the blood and on examination of the urine. This operation is disappointing in its effect on the blood pressure, but nevertheless the patient's symptoms are lessened and the condition of his fundi is improved. Splanchnectomy produces its effect possibly by several methods, denervation of the splanchnic vessels and the adrenals and the relief of renal ischæmia. It is probable that a large denervated vascular area is produced, which acts as a safety valve, thus relieving the patient of sudden changes in the blood pressure. A section of the eleventh rib near the spine was removed and the sympathetic chain was exposed. The ninth, tenth, eleventh and twelfth thoracic ganglia were removed, and also sections in the greater, lesser and least splanchnic nerves. An initial fall of blood pressure usually occurred, followed by a rise approaching the pre-operative level.

The Value of the Mantoux Reaction in Ocular Tuberculosis.

M. SCHLICHTING (*Klinische Monatsblätter für Augenheilkunde*, April, 1940) holds that, as clinical tests, the inoculation of portion of the affected tissue and a positive focal reaction in the eye to a diagnostic tuberculin injection are alone to be regarded as reliable. He admits that these tests can be rarely used. He endeavoured to determine the value of skin responses to a series of graduated injections given by 87 patients with probable ocular tuberculosis and by an equal number of patients definitely free from an active lesion. He found there was no essential difference between human and bovine tuberculin with regard to their effect, that the reactions of the two groups of patients were not essentially different, and that the majority of the tuberculous patients failed to react or reacted only to higher concentrations. Intracutaneous tuberculin reactions therefore do not appear to clarify the tuberculous ætiology of ocular disease.

Cyclodiathermy Puncture in Glaucoma.

A. VOGT (*The British Journal of Ophthalmology*, June, 1940) advocates cyclodiathermy in obstinate cases of glaucoma, when other operations have failed and when the anterior chamber has disappeared. To avoid damage to the lens and other structures the needle must not be longer than 0·5 millimetre or thicker than 0·18 millimetre, and punctures must not be made over an area of 2·5 millimetres from the limbus. An incision in the conjunctiva is made over the insertion of the inferior rectus extending to the insertions of the internal and external recti. The conjunctiva being cleared sufficiently, a girdle of 2·5 millimetres (embracing the inferior rectus insertion) is punctured with the diathermy needle as far as the internal and external recti, 60 milliamperes of current being used. The needle stays in for half to one second.

Convergence Deficiency.

I. MANN (*The British Journal of Ophthalmology*, August, 1940) deals with a small group of cases characterized by the fact that they show a deviation of 6° or more (exophoria) in the Madden wing test and that when the patients are ordered to converge voluntarily without an object to fix upon, they are totally unable to perform the movement. This latter sign is of the greater importance. These patients complain of being unable to read without difficulty and pain, in spite of wearing the correction for their respective error, which is insignificant. It is well known that by practice individual muscles, which usually act reflexly or in association with other muscles, may be made to contract voluntarily. The contraction of both internal recti to produce convergence may never be under voluntary control, but occurs in association with accommodation and the fixation reflex. Voluntary control is acquired normally at about the age of six, but may be delayed. In treatment two methods of approach are possible. The power and amplitude of the reflex can be increased until it becomes conscious, or the patient can be shown how to perform the voluntary action first and to relegate it to the level of a reflex when it has been mastered. The first method includes the performance of exercises in fusion on the synoptophore and exercises with prisms and a stereoscope. The second method is preferable, and the author uses both. In a dark room with a lighted candle the patient is taught to see the double light when fixing his finger, and the double finger when fixing the light. By stages he is taught to see the double light even when the finger is not present, thus accomplishing voluntary convergence. Printed directions are given to the patient. The author considers convergence deficiency among the most easily treated of the heterophorias.

Operation for Spastic Entropion.

R. E. MEELE (*Archives of Ophthalmology*, September, 1940) describes the following operation for spastic entropion. An incision is made in the entire length of the lid three millimetres from the margin. The lower flap is undermined for three millimetres, the upper for one millimetre. Two flaps of orbicularis muscle, each four millimetres in width, tapering at each end, are dissected from the tarsus, an attachment to the tarsus being left over an area of seven millimetres at the centre. An incision is made slightly temporal down to the anterior surface of the inferior orbital margin. With "000" plain catgut passed through the periosteum the temporal muscle flap is loosely sutured here. The nasal muscle flap is similarly sutured to the periosteum slightly to the nasal side. The skin is then sutured.

OTO-RHINO-LARYNGOLOGY.

The Connective Tissue of the Neck.

J. D. WEINTRAUB (*Archives of Otolaryngology*, January, 1941) proffers a new description of the connective tissues of the neck and gives a special description of the post-pharyngeal spaces. Rather than accept the standard previous description of the gross connective tissue of the neck as forming three principal planes of cervical fascia, the author, basing his contentions upon the observations of seven years in the dissecting room, prefers to describe the connective tissues as having a uniform systematic arrangement, relative to the viscera, the blood vessels and muscles. Thus he describes a periorgan and a perimuscular condensation of connective tissue surrounding viscera and muscles respectively, and areolar tissue spaces—shearing tissues—between various organs and muscles, to allow movement between one another. The author describes a principal nerve-vessel connective tissue associated with the carotid artery and internal jugular veins, and passing from this with the branching vessels and nerves, nerve-vessel sheets. The areolar tissue spaces

are limited partly by the nerve vessel sheets and partly by the points of muscular attachment. Three areolar shearing spaces are described behind the myo-pharyngeal tube. In the first place, in the peripharyngium itself there is a pair of right and left juxtamedian peripharyngeal spaces. These extend from the roof of the pharynx to the beginning of the œsophagus. They are separated from one another by a well-defined median fibrous septum. An abscess in one of these spaces is therefore in the wall of the pharynx and is not truly retropharyngeal. The lateral retropharyngeal lymph nodes lie medial to the internal carotid artery and in close relation to the upper and lateral aspect of the peripharyngeal spaces, but not in the space. Secondly, behind the peripharyngeal fibrous thickening, and thus behind the symmetrical spaces described, lies a wide unpaired postvisceral space, occupying and spreading across the mesial plane. This is described as a very loose space, and it extends downwards into the mediastinum. An abscess on this space, as distinct from that of the previously described peripharyngeal spaces, tends to cross the mid-line and may rapidly reach the mediastinum. Thirdly, the perimysial connective tissue thickening surrounding the prevertebral muscles on each side includes a further pair of areolar spaces, prevertebral perimysial spaces, right and left. It is into these spaces that pus from caries of a vertebral body may break and thence spread along the muscles downwards and laterally towards the lateral triangle of the neck and perhaps into the thorax.

S. IGLAUER (*ibidem*) confirms the conclusions of Weintraub and the existence of three sets of post-pharyngeal spaces and describes the clinical course and post-mortem examination of two cases in which an abscess formed in one of the paired peripharyngeal spaces described by Weintraub. In these cases infection appeared to have resulted from breaking down of the lateral retropharyngeal lymph glands. In one case erosion of the common carotid artery had taken place and in the other there had been rupture into the pharynx and considerable necrosis of the pharyngeal wall.

The Lothrop Operation for Chronic Frontal Sinusitis.

O. A. LOTHROP (*Archives of Otolaryngology*, January, 1941) reports his conclusion on the frontal sinus operation first described twenty-five years ago by H. A. Lothrop and himself. The operation, which is recommended for chronic cases of frontal sinusitis in the quiescent stage, is a combination of an external approach and the intranasal rasp operation. The objects are complete removal of diseased mucosa from the frontal sinus and its recesses and the establishment of a bone-supported duct leading into the nose. The author contends that without this bone-supported duct there is a tendency for soft tissues to prolapse into the passage-way leading to the nose, thus obstructing drainage. Through the external opening it is possible to watch the action of the rasp, which is then used to remove the thick bone at the base of the frontal and nasal bones and some of the nasal process of the maxilla. Removal of the anterior half of the middle turbinate, exenteration of the anterior ethmoidal cells and any correction of a deviated septum are carried out several months before the principal operation on the frontal sinus. Such an allowance of time permits this area to undergo epidermization so that there is an epithelial surface ready to spread over the area to be exposed by the external operation and rasping process.

Surgical Treatment of Bilateral Paralysis of the Abductor Muscles of the Larynx.

JOSEPH D. KELLY (*Archives of Otolaryngology*, February, 1941), after reviewing the evolution of methods for the restoration of a natural airway in paralysis of the abductor muscles of the larynx, outlines the operation devised by B. T. King in which efforts were made to bring about abduction of the arytenoid and vocal cord on one side by transplanting the anterior belly of the omohyoid muscle to the arytenoid cartilage. The advantages seen in this operation were that surgical interference was entirely extralaryngeal, thus avoiding the formation of scar tissue, and, as it preserved the tissues of the larynx, the chances that the patient would have a good voice were increased. It is pointed out that King further improved his own technique by completely mobilizing the arytenoid cartilage by cutting it practically free from the articular process of the cricoid cartilage. Later still, King, observing that his greater number of successful results comprised cases in which he completely mobilized and displaced outwards the arytenoid cartilage, has come to the conclusion that it is this displacement of the arytenoid which brings about improvement of the airway, and he therefore proposes to abandon the omohyoid transplantation. Convinced of the value of this arytenoid displacement, the author describes an operation in which he approaches the arytenoid through a window made in the posterior third of the thyreoid ala and by careful dissection is able to remove the entire arytenoid cartilage without making an opening into the laryngeal cavity. He reports two cases in which this procedure has been carried out, and in both a satisfactory airway was established, and in addition the patient retained a good useful voice. An illustration of the larynx of one patient, two months after operation, shows that quite a wide space develops between the posterior ends of the vocal cords, owing to removal of the arytenoid on one side.

The Diagnosis and Treatment of Tuberculosis of the Lungs and Contiguous Areas.

GEORGE E. WILSON (*Archives of Otolaryngology*, February, 1941) reports his experiences with data and conclusions based on over 1,000 tuberculous patients encountered in eight years of private practice. In 672 of these cases there was laryngeal involvement. Except in cases with very minor lesions the writer is a strong advocate for local treatment, combined, of course, with routine management of the pulmonary condition. Trial was given with various applications, such as gynocardic acid, lactic acid, trichloracetic acid and many others. The author regards the galvanic cautery as superior to all other forms of treatment and recommends this procedure as a routine in all cases except those with minor lesions, in which he finds it unnecessary, and in a limited number of cases in which the acuteness or severity of the general condition contraindicates any mechanical or local interference. The larynx is viewed for this procedure by the indirect mirror method. Sharp-pointed electrodes, heated to a white heat to avoid sticking and hæmorrhage, are employed. Four to eight punctures, about one-eighth of an inch apart, and of similar depth, are made into the diseased sites. The procedure is repeated at two to four week intervals over a period of three months to one year, the aim being to extend the applications gradually to cover all involved parts. Bronchoscopic examination, which appears to be more frequently resorted to in tuberculosis by American surgeons than in most other parts of the world, has been of value in identifying and treating certain lesions in the trachea and bronchi. The application of silver nitrate, 10% to 20%, has been of value in some of these cases.

Chronic Sinusitis and Bronchial Asthma.

R. CLARK GROVE (*New York State Journal of Medicine*, March 1, 1941) gives figures of the incidence of nasal sinusitis in cases of asthma. He also raises again evidence that the infection in many of these cases is actually in the substance of the sinus mucosa, so that "negative" washings are not proof of the absence of sinusitis. Diagnosis is based upon careful history taking and on clinical and X-ray examinations. When it is established that sinus disease is present, operation is recommended, and this, the author stresses, must be radical and thorough. Allergic testing and treatment are regarded as necessary in addition to surgical measures. Two hundred patients suffering from asthma with disease of the paranasal sinuses who were treated surgically are mentioned. In 69·5% of cases definite improvement was recorded. The condition of 85% of those who received complete surgical treatment was improved as contrasted with only 54% showing improvement in the group which had only partial surgery. The author insists that the improvement may not be immediate, since some infection may remain in the cervical and bronchial lymphatic glands, and this may take some little time to be eliminated. During this period attention is given to allergen testing and treatment. This should include the use of autogenous vaccines.

Results of Treatment of Tuberculosis in the Trachea and Bronchi.

J. D. KERNAN AND A. J. CRACOVANER (*New York State Journal of Medicine*, March 1, 1941) report the results of bronchoscopic investigation and treatment of tracheo-bronchial tuberculous lesions. It is pointed out that a granuloma at the entrance to a branch bronchus may interfere with drainage or with the securing of full benefits from collapse therapy. Through the bronchoscope this obstructing piece of tissue may be removed. For ulceration and lesser granulations applications of a 10% solution of silver nitrate have been found to be of great value. The use of ultra-violet rays from a mercury vapour lamp were also found to be of value. Best of all was a combination of ultra-violet ray treatment and silver nitrate.

British Medical Association News.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held on May 7, 1941, at the Medical Society Hall, East Melbourne, DR. H. BOYD GRAHAM, D.S.O., M.C., the Acting President, in the chair.

Cryptotrophic Factors in Nutrition.

EMERITUS PROFESSOR W. A. OSBORNE read a paper entitled "Cryptotrophic Factors in Nutrition" (see page 747).

SIR JAMES BARRETT related several experiences in which he had been made aware of the importance of cryptotrophic factors in nutrition. At the Kuala Lumpur Research Institute on the Malay Peninsula 95 fowls fed on polished rice had developed peripheral neuritis. The experiment had a bearing on the question whether Japanese labourers, who were prone to contract beriberi, should be fed with polished or unpolished rice. Sir James Barrett then referred to another occurrence when he was in Palestine; pellagra had been rampant among the 140,000 Turkish prisoners. That fact was brought to notice in a curious way; the undertakers were paid one pound for each dead Turk, and on receipt at headquarters of a bill for £60 from one undertaker, General Allenby decided that something had to be done. Sir James Barrett was consulted and a scientific committee was appointed to make an investigation. It was recognized that there was a stage at which a cure could be effected and a stage beyond which the condition proved fatal. It was an unequalled opportunity, as all the work could be done under military control and was of urgent importance, since the disastrous effects of the disease and the blindness were likely to cause political uproar. Within forty-eight hours of the making of the decision the personnel of the commission was gazetted and a preliminary report was demanded within six weeks; in three months the cause of the trouble was found. The Turks died of dysentery or tuberculosis as an infection incurred while they were in a condition of food deficiency; they had lived on dry bread and dates and had been chivvied about the country by the advancing enemy. The dividing line between curability and death was the onset of the collateral infection.

Sir James Barrett then referred briefly to scurvy in the days of Captain Cook. Cook's ships had reached Batavia with the loss of only one man, but afterwards he lost many because of infection with malaria and dysentery.

Finally, Sir James Barrett spoke on the subject of dental decay and dietary. He said that predynastic Egyptians had sound teeth, but with the introduction of cereals as food the same could not be said of the Egyptians of the times of the Pharaohs. Aboriginal Australians, Hawaiians and Maoris who lived on fresh food did not have caries, which appeared whenever those peoples ate civilized modern food. He added, however, that he agreed with Professor Osborne that natural selection could by no means be overlooked as a factor in the production of dental caries.

DR. W. OSTERMEYER expressed his appreciation of the inclusion on the notice paper of the meeting of a summary or synopsis of the lecture; it enabled members to come prepared to follow the lecturer more closely and to appreciate more accurately the views he expressed.

DR. F. L. TRINCA, after thanking Professor Osborne for his address, asked him some practical questions. The soldiers at Gallipoli had developed a condition resembling "Barcoo rot" when they were receiving a dietary of bully beef and biscuits; this had cleared up within two months on the beaches when they were given good nutriment. The troops in the desert, when changed from a full diet to bully beef and biscuits, had suffered from diarrhœa. Dr. Trinca asked Professor Osborne whether sudden alterations of dietary were likely to accelerate trouble. Speaking as one who could claim long contact with sick people, Dr. Trinca expressed the view that disordered action of the heart was produced by homologous infection affecting the myocardium. Since 1921 he had advised the feeding of patients suffering from rheumatoid arthritis along the generous lines advocated in tuberculous conditions; hitherto rheumatoid arthritis had been regarded as a "wear-and-tear" disease, and the dietary had been based on that theory. He then referred to an article in which dental caris was attributed to lack of lime. Dr. Trinca went on to speak of the use of preparations of the spleen in therapy; the spleen was an inhibitory gland with a secretion that inhibited the activity of other hormones, and had for a long time been regarded as poisonous; but Dr. Trinca wondered whether it might have an appropriate place in treatment of certain disorders of the glands.

DR. JOHN DALE said that Professor Osborne's paper was interesting and enlightening. He went on to say that it was an important part of his work as medical officer of health of the city of Melbourne to interpret to the public the advances of science. He had taken it that Professor Osborne, in his statement that natural selection operated by bringing about the degeneration of teeth, meant gradual atrophy and reduction in number or disappearance of some of the teeth rather than disease and caries. Dental disease at all ages was a serious problem among modern civilized nations, and had its origin in dietetic factors; it could be referred broadly to the enormous increase in modern times in the consumption of white flour and sugar. Dr. Dale remarked that evidences of caries had been found in the teeth of Pharaohs, but not in those of the *fellaheen*, who lived much more simply. Dr. Dale said that he would be sorry if the members of the profession failed to support the idea that roller-milled white flour was dangerous. Among the poorer section of the community the question mattered a great deal. Farmers' wives during hard times in the wheat belt in the western districts had been forced to make their families subsist on damper made from whole flour and kangaroo meat, and the teeth had not suffered. He recommended for study the book by Drummond and Wilbraham entitled "The Englishman's Food"; in it appeared analyses of the loaf made from stone-ground flour and that from high extraction roller flour, which showed that in about five different respects the stone-ground flour loaf was much the better. It contained more vitamin *A*, vitamin *B*, riboflavin, iron and calcium.

Dr. Dale had been interested in Professor Osborne's reiteration that bran was irritating to the colon; it certainly appeared to be in individual cases, but he very much doubted whether the doctrine was of general applicability. The loaf made of what was called wholemeal had only 5% of the bran extracted. He added that the "Dale" loaf was made of that flour with skimmed milk; it was not unpleasant, and certainly was not irritating to the intestine. Wholemeal crusts were commonly used as the only cereal immediately after weaning in infancy, on the advice of experts; it was hard to believe that they were irritating.

DR. R. L. FORSYTH said that he could assure Professor Osborne that in a long professional life he had met with very few people who could not tolerate bran. For ordinary civilized parous women he had had singular success with it, and he had given them much of it. He knew that he was ignorant of many things, but he had had some experience in that matter. He remembered that someone in France, one-third of a century earlier, had started to give injections of sea-water secured from some distance off the shore; perhaps it would be a reasonable idea to use diluted sea-water instead of normal saline solution in therapy.

DR. IVAN CONNOR confessed that he did not like wholemeal bread, and gave a brief description of how to make a damper from home-ground wheat.

DR. MILDRED HUTCHINGS described how to cook wholemeal bread as it was done in the country.

DR. R. T. ALLAN said that at Nauru the elderly people were fine specimens, with good physique and perfect teeth, but the young people were spoiled; they had poor teeth at an early age, and were subject not only to dental caries, but to appendicitis, gall-bladder troubles and gastric and duodenal ulceration. The older folk did not reject the old diet of coconuts and fish; but the young people had more money to spend and spent it on tinned foods, showing a predilection for such things as salmon and pears. Dr. Allan added that when he was in China he had noticed that although beriberi was caused by the polished rice, the natives took a long while to learn by experience and had to be forced to use whole rice instead.

PROFESSOR R. D. WRIGHT said that it had been pleasant to sit once more at the feet of his old master and to listen again to his characteristic happy phrases and succinct expressions. He had no quarrel with any of Professor Osborne's statements, but he took the opportunity to mention the history in Australia of the investigation of trace elements. At the health laboratory in South Australia the effects of copper deficiency had been investigated by the cooperation of laboratory workers and veterinary officers as field workers. There was a disease known in South Australia as coast disease, of which sheep pined and died; the condition was known as pine disease in Scotland, and it had been found that the addition of minute traces of cobalt to the dietary cleared it up. In another disease of sheep the wool became coarse and shiny; it was known as bright, steamy or doggy wool, and was due to copper deficiency caused by the burning off of the scrub. In the case of cobalt it was not yet possible to develop an artificial diet to produce cobalt deficiency disease. It should not be

forgotten that on occasions investigators might be dealing with some local anomaly where there just happened to be a deficiency. They should all be conscious of the possibility of ignorance and of the possibility of overcoming that ignorance by cooperation between laboratory and field workers.

Professor Osborne, in reply, observed that the critics had let him off very lightly. He had had no idea of the massiveness of the outbreak of pellagra in Palestine to which Sir James Barrett had referred. He reminded Dr. Ostermeyer that Ejikman had at one time thought that there was a toxin in the unpolished rice and a corresponding antitoxin in the polishings. In reply to Dr. Trinca, Professor Osborne said that it had interested him to hear about digestive disturbances caused by a change of dietary. It might not be generally known that ascorbic acid tablets had been issued to the men of the British Navy to replace fresh citrus fruit, but the issue had had to be stopped, because it was said that the tablets caused diarrhœa. Most people realized that certain instincts came into play as the passenger reached a port; there was a mild revolt against the ship's diet, and even buns at Fremantle were a delight.

Professor Osborne emphasized the objection to the use of inadequately descriptive synonyms for the vitamins, such as "growth-promoting" or "protecting against infection"; these, as Professor C. J. Martin had said, should not be tagged onto any particular vitamin. Professor Osborne then amplified what he had said about dental caries. Lack of vitamin *D* undoubtedly aggravated decay, but it was not the only cause of it; by the action of natural selection teeth were bound to go, as had the snake's legs. He was in agreement with Dr. Dale that when white bread predominated in the dietary evidences of deficiencies might be forthcoming; it appeared to him, however, preferable to make good the deficiency in some other way than by the use of wholemeal in the bread.

In 1904 Professor Osborne had been struck with the high incidence of acne among the young people he met in the classrooms and elsewhere, but he did not think the condition was nearly so prevalent nowadays. He had wondered whether it was a nutritional matter or whether the improvement was due to a lack of smoke in the air and a diminution of the city dust. On the subject of bran, Professor Osborne had been informed that he was in a hopeless minority; yet veterinary experiences were in support of the attitude he had adopted. When bran was given to horses, pigs and other animals it went right through them; the amount of bran had to be cut down and that of the pollard increased to fatten them. Professor Osborne said that if a "drug" had to be used, he preferred "Eno's Fruit Salts".

Commenting on Dr. Forsyth's suggestion that sea-water might be tried instead of normal saline solution in therapy, Professor Osborne reminded him that the sea had altered somewhat since it first entered the body fluids of animals; the chief difference was the greater concentration of magnesium salts. He then observed that instinct was a wonderful thing, and did much more than was generally recognized to determine nutritional requirements; people distributed the Calories over proteins, carbohydrates and fats with similar instinctive certainty to that shown by a bird in building its nest. In conclusion, Professor Osborne repeated that, as Professor Wright had said, the laboratory and field workers should come together more often. A big problem awaiting solution was the decision as to whether the trace element was in the plant or only in the soil—whether it ascended into the cell cytoplasm or merely inhibited soil bacterial growth or in some other external way acted beneficially on nutrition.

Medical Societies.

THE MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING of the Medical Sciences Club of South Australia was held at the University of Adelaide on October 4, 1940.

The Digestibility of Nitrogen Compounds in the Sheep.

MR. E. W. LINES presented a paper entitled "The Digestibility of Nitrogen Compounds by the Sheep". He pointed out that if crude protein digestion was measured in terms of nitrogen, the percentage digestibility as usually defined by the formula $\frac{\text{(Ingested N} - \text{Fæcal N)}}{\text{Intake N}}$ did not represent the actual digestibility because (*a*) increasing crude protein intake increased the conventional digestibility, and (*b*) wool growth corresponded more accurately with intake N than with either "digestible N" or urinary N. The ratio (wool N) : (ingested N – fæcal N) occasionally reached the astonishing value of 40%.

The saliva of a 40-kilogram sheep amounted to something like eight litres per day and contained about one milligramme of nitrogen per millilitre, two-thirds of which was non-protein nitrogen. There was thus a return to the digestive tract of some eight milligrammes of nitrogen per day, while normal fæcal nitrogen was in the range of 3·5 to 5·0 grammes per day. There was thus reasonable grounds for the assumption that in the sheep most of the fæcal nitrogen was of endogenous origin and represented protein which had been metabolized, and not undigested protein.

Ophthalmic Conditions.

DR. T. L. MCLARTY showed a film, belonging to Dr. Godsall, which was made available by the courtesy of the South Australian Branch of the British Medical Association. The film was in colour and demonstrated the technique of corneo-scleral sutures in cataract extraction.

This was followed by a short account of two cases of congenital coloboma of the iris. In one case the abnormality, from the family history, was behaving as a recessive characteristic, while in the other it appeared, as is more usual, as the dominant form.

Dr. McLarty pointed out that accompanying abnormalities were not infrequent and that glaucoma was a common occurrence in eyes in which the congenital defect amounted to aniridia. He concluded by explaining that the most generally accepted theory accounting for the defect was that due to Hess, who concluded that persistent remnants of the fibro-vascular sheath of the lens offered a mechanical hindrance to the developing iris.

Medical Practice.

THE NEW ZEALAND SOCIAL SECURITY ACT.

IN the issue of April 5, 1941, we published for the information of members the regulations recently made by the Government of New Zealand in connexion with the *Social Security Act*, 1938 (as amended by Part II of the *Finance Act*, Number 4, 1940). We now publish *in extenso* the regulations relating to the drug tariff and pharmaceutical supplies under the same act.

The Social Security (Pharmaceutical Supplies) Regulations 1941.

1. These regulations may be cited as the Social Security (Pharmaceutical Supplies) Regulations 1941.

Definitions.

2. In these regulations, unless the context otherwise requires,—

"The said Act" means the Social Security Act, 1938:

"Appointed date" means the date appointed by the Minister, pursuant to clause 3 hereof, as the date on and after which prescribed medicines and other pharmaceutical requirements will be available in accordance with these regulations to persons who are entitled to receive pharmaceutical benefits in accordance with the said Act:

"Appropriate Committee" means a Committee appointed or recognized by the Minister for the purposes of these regulations, in accordance with section 83 of the said Act:

"Drug tariff" means the drug tariff for the time being in force in accordance with these regulations:

"Department" means the Department of Health established under the Health Act, 1920:

"Health district" or "district" means a health district constituted under the Health Act, 1920:

"Medical Officer of Health" means a Medical Officer of Health under the Health Act, 1920:

"Medical practitioner" means a medical practitioner registered under the Medical Practitioners Act, 1914:

"Minister" means the Minister of Health:

"Pharmaceutical requirements" includes all such medicines, drugs, appliances and materials as are included in the drug tariff for the time being in force under these regulations.

Commencement of Benefits.

3. (1) The Minister shall appoint a date on and after which the benefits provided for by these regulations will be available for persons who are entitled to receive pharmaceutical benefits in accordance with the said Act.

(2) Notice of the appointed date shall be published in the *Gazette* and in such other manner, if any, as the Minister thinks fit.

The Drug Tariff.

4. (1) The Minister shall, for the purposes of these regulations, prepare a drug tariff, which shall contain, in addition to such other particulars as the Minister thinks fit, the following particulars, namely:

(*a*) The names or descriptions, either specific or general, and standards of quality, of the medicines, drugs, appliances, and other materials that are for the time being the subject-matter of the benefits provided for by these regulations:

(*b*) The prices to be paid out of the Social Security Fund for such pharmaceutical requirements as are supplied in accordance with these regulations, or the methods of computing the prices to be paid for such requirements:

(*c*) The services or things for which additional fees, to be paid out of the Social Security Fund, may be paid to persons supplying pharmaceutical requirements in accordance with these regulations, and the amount of such additional fees or the method of computing such additional fees.

(2) Provision may be made in the drug tariff prescribing the maximum quantities of any specified pharmaceutical requirements that may be supplied in accordance with these regulations pursuant to any one medical prescription or other order.

(3) The drug tariff may be at any time amended by the Minister, after consultation with the appropriate Committee, in such particulars as he thinks fit.

(4) If any dispute arises as to the true meaning and application of any terms used in the drug tariff, the Minister, after consultation with the appropriate Committee, may determine the dispute in such manner as appears to him just, and his decision thereon shall be final.

(5) Copies of the drug tariff and of every amendment thereof shall be supplied, free of charge, to every person who has undertaken to supply pharmaceutical requirements in accordance with these regulations.

Supply of Pharmaceutical Requirements.

5. (1) The proprietor of any pharmacy within the meaning of the Pharmacy Act, 1939, may, by a notice of acceptance in the form No. 1 in the Schedule hereto or to the like effect, undertake to supply pharmaceutical requirements in accordance with these regulations to persons entitled to receive the same.

(2) Any person, other than the proprietor of a pharmacy, who is entitled to sell any drugs or other pharmaceutical requirements may, by a like notice, with the concurrence of the Minister, and subject to such conditions, if any, as the Minister may impose, undertake to supply pharmaceutical requirements or any specified kind or class of pharmaceutical requirements in accordance with these regulations.

(3) Every notice under this clause shall be delivered or sent to the Medical Officer of Health of the appropriate district.

(4) Every proprietor of a pharmacy or other person who undertakes to supply any pharmaceutical requirements in accordance with these regulations is hereinafter in these regulations referred to as a "contractor".

Obligations of Persons who have Undertaken to Supply Pharmaceutical Requirements.

6. (1) Every contractor, as defined in the last preceding clause, who is the proprietor of a pharmacy shall be required to keep open for business, during the times specified in his notice of acceptance, the place or the several places of business referred to therein. On the outer door or window of each such place of business he shall at all times keep prominently displayed a notice in the form No. 2 in the Schedule hereto or to the like effect.

(2) For the purpose of enabling him to comply with his undertaking to supply pharmaceutical requirements every contractor who is the proprietor of a pharmacy shall, as far as practicable, keep in stock a sufficient supply of all such medicines, drugs, appliances, and other materials (if any) as are specified in the drug tariff as being required to be kept in stock.

7. (1) In this clause the expression "medical prescription" means a prescription or order signed on or after the appointed date by any medical practitioner, prescribing pharmaceutical requirements for any person who is entitled to receive pharmaceutical benefits under the said Act.

(2) On presentation to a contractor under these regulations of any medical prescription, and on compliance by the customer with the requirements of clause 9 hereof, it shall be the duty of the contractor, with all reasonable promptitude and in accordance with the terms of the prescription, to supply the pharmaceutical requirements prescribed in the prescription.

8. In this clause—

The expression "authorized midwifery pharmaceutical requirements" means such pharmaceutical requirements, if any, as are specified in the drug tariff to be obtainable on the presentation of a midwifery order:

The expression "midwifery order" means an order for the supply of any authorized midwifery pharmaceutical requirements to or on behalf of a woman who has made arrangements with the licensee of a licensed maternity hospital or with an obstetric nurse to obtain maternity benefits in accordance with the provisions of the Social Security (Maternity Benefits) Regulations 1939.[1]

(2) Every midwifery order under this clause shall be signed by the licensee or manager of the hospital or by the obstetric nurse, as the case may be, and shall be countersigned by the Medical Officer of Health of the district.

(3) Except in cases of emergency, every midwifery order shall be countersigned as aforesaid before being fulfilled by a contractor in accordance with the next succeeding subclause.

(4) On presentation to a contractor under these regulations of a midwifery order, and on compliance by the customer with the requirements of clause 9 hereof, it shall be the duty of the contractor to fulfil the order with all reasonable promptitude.

9. (1) Where any prescription or order is presented to a contractor under these regulations by the person to whom it relates, the contractor shall require the customer to sign the prescription or order and to add to his or her signature the date of the presentation of the prescription or order, and also his usual place of residence if it does not already appear on the prescription or order.

(2) Where a prescription or order is presented to a contractor by any other person, the contractor shall require the customer to state on the prescription or order the name and usual place of residence of the person to whom it relates (if those particulars do not already appear on the prescription or order) and also to sign the prescription or order, and to add to his or her signature the date of the presentation of the prescription or order.

(3) Every prescription or order presented to a contractor under these regulations shall be surrendered to the contractor and shall be dealt with by him in accordance with clause 14 hereof.

(4) Where, in accordance with express directions contained in any medical prescription, the medicine prescribed therein is to be supplied on more occasions than one, the person taking delivery of such medicine on each separate occasion shall give to the contractor a receipt therefor bearing the date of the delivery of the medicine.

10. Where any contractor under these regulations has undertaken to supply only specified kinds or classes of pharmaceutical requirements, nothing in the foregoing provisions of these regulations shall be construed to impose on him an obligation to supply pharmaceutical requirements of any other kind or class.

Lists of Persons who have Undertaken to Supply Pharmaceutical Requirements.

11. (1) For every health district there shall be compiled a list of the persons carrying on business in the district who have undertaken to supply pharmaceutical requirements in accordance with these regulations.

(2) Every such list shall be in such form as the Minister may direct or approve and shall be amended from time to time as occasion requires.

(3) Copies of such lists shall be open to inspection by the public during office hours at the office of the Medical Officer of Health, and at such other places, if any, as the Minister thinks necessary for the information of persons concerned.

[1] Statutory Regulations 1939, Serial number 1939/43, page 207. Amendment No. 1: Statutory Regulations 1939, Serial number 1939/92, page 382.

(4) The list shall, in respect of each contractor whose name is included therein, contain particulars of—

(*a*) His place or places of business:

(*b*) The times during which the several places of business are open:

(*c*) In the case of a contractor who has undertaken to supply only specified kinds or classes of pharmaceutical requirements, the kinds or classes so specified.

Termination by Contractors of Undertaking to Supply Pharmaceutical Requirements.

12. (1) No person who has undertaken to supply any pharmaceutical requirements in accordance with these regulations shall, except with the leave of the Minister, be entitled to terminate his undertaking except on three months' written notice of intention to terminate the undertaking given to the Medical Officer of Health.

(2) Notwithstanding anything in the last preceding subclause, a contractor under these regulations shall not be entitled, except with the leave of the Minister, to terminate his undertaking under these regulations at any time while an investigation concerning him is pending under section 84 of the said Act.

Remuneration of Persons Supplying Pharmaceutical Requirements.

13. (1) Where, on or after the appointed date, any contractor supplies any pharmaceutical requirements in accordance with these regulations for the use of a person who is entitled to receive pharmaceutical benefits under the said Act, he shall be entitled to receive payment out of the Social Security Fund of an amount to be assessed by the Department, being the equivalent of the price of the goods supplied, computed in accordance with the provisions of the drug tariff, and of any additional fees authorized by the drug tariff.

(2) The price so computed shall be the price as at the pharmacy or other place of business of the contractor, and any expenses incurred by the contractor by way of postage or otherwise in delivering any goods at any other place shall be payable to the contractor by the person to or for whom such goods were supplied. Where any pharmaceutical requirements are to be delivered by post, the contractor may require prepayment of the postage. If in any case prepayment of postage is impossible or impracticable, the goods may be posted subject to the condition that the postage and any additional fees charged by the post-office for delivery will be payable on delivery.

(3) Except as provided in the last preceding subclause or as otherwise expressly provided in the drug tariff, the amount paid to a contractor out of the Social Security Fund in respect of any pharmaceutical requirements supplied by him shall be accepted by him in full satisfaction of all claims in respect thereof.

14. (1) All claims for payment in respect of pharmaceutical requirements supplied by contractors under these regulations shall be made in the first instance to the Medical Officer of Health of the district in which the contractor carries on business.

(2) Every such claim shall be accompanied by the prescriptions or orders referred to in the claim, and shall be supported by such receipts, certificates, or other documents as may be required in proof of the supply by the contractor of the pharmaceutical requirements to which the claim relates:

Provided that the production of any such receipts or other documents may be dispensed with in any case if the Department is satisfied that, owing to special circumstances, it was not practicable for the contractor to obtain or produce them.

(3) On every prescription or order forwarded with any claim under this clause the contractor shall, if required by the Department so to do, furnish his own computations, in detail, of the amount that he is entitled to receive from the Social Security Fund in respect thereof.

(4) Where the particulars required by clause 9 of these regulations are duly supplied on any prescription or order forwarded with any claim, the prescription or order shall, in the absence of evidence to the contrary, be deemed to have been duly fulfilled for the benefit of a person entitled in accordance with these regulations to receive the pharmaceutical requirements referred to therein.

15. (1) On application in that behalf by any contractor, the Department shall afford to the contractor reasonable facilities for examining the prescriptions or orders forwarded by him in respect of any claims, and also for examining the computations made by the Department in assessing the prices and fees payable in respect thereof.

(2) Similar facilities shall, on application, be afforded to duly appointed representatives of the Pharmacy Board of New Zealand, or of the Chemists Service Guild of New Zealand, or of the appropriate Committee appointed under section 83 of the said Act.

Special Provisions affecting Hospital Boards.

16. (1) Nothing in these regulations shall apply with respect to the supply of any pharmaceutical requirements prescribed for in-patients of any public hospital or other institution maintained by a Hospital Board.

(2) Where any pharmaceutical requirements prescribed for out-patients of any public hospital are supplied by the Hospital Board, the Board shall be entitled to receive payment therefor as if it were a contractor within the meaning of these regulations.

Miscellaneous.

17. (1) Any person who is entitled in accordance with these regulations to claim from any contractor any pharmaceutical requirements for himself or for any other person may make a complaint in writing to the Medical Officer of Health:—

(*a*) If, on presentation of any prescription or order, the contractor refuses or fails, contrary to the provisions of these regulations, to supply any pharmaceutical requirements in accordance with the prescription or order; or

(*b*) If, in the supply of pharmaceutical requirements in accordance with any medical prescription, the contractor has displayed any culpable negligence or lack of care.

(2) Unless in the opinion of the Medical Officer of Health the complaint is trivial, he shall refer it for investigation and report to a committee appointed by the Minister pursuant to section 83 of the said Act for the purpose of hearing complaints.

(3) Any complaint that is regarded by the Medical Officer of Health as trivial shall nevertheless be referred by him to the Minister if the complainant so requires, and if the Minister is of opinion that the complaint is well founded and is sufficiently serious, he shall refer it to the Committee appointed to hear complaints.

18. (1) If any person having undertaken to supply pharmaceutical requirements in accordance with these regulations wilfully fails or refuses, contrary to the provisions of these regulations, to supply any person entitled thereto with any such pharmaceutical requirements, he shall be liable to a penalty not exceeding £10, which shall be recoverable by way of deduction from any moneys payable to him from the Social Security Fund in accordance with these regulations.

(2) Any penalty under this clause may be imposed by the Minister on the recommendation of the appropriate Committee and not otherwise.

Drug Tariff under the Social Security (Pharmaceutical Supplies) Regulations 1941.

1. This instrument, which has been prepared in accordance with the regulations referred to above, may be cited as "the Drug Tariff 1941".

2. For the purposes of the Drug Tariff:—

"Official Pharmaceutical Publication" means the British Pharmacopœia (1932) (including the Addenda thereto of 1936 and 1940), and the British Pharmaceutical Codex (1934):

"The Rules for Prescription Pricing" means "the Official Schedules and Rules for Prescription Pricing" issued by the Pharmacy Plan Industrial Committee under the authority of the Industrial Efficiency (Pharmacy) Regulations 1938 (including any amendment thereof that may hereafter be made or any document that may hereafter be issued in substitution therefor):

"The Fund" means the Social Security Fund:

"The said regulations" means the Social Security (Pharmaceutical Supplies) Regulations 1941.

3. (1) Except as otherwise provided in the next succeeding subclause, all drugs, medicines, and medicinal preparations of which a monograph or formula is published in any official Pharmaceutical Publication shall be included in the expression "Pharmaceutical requirements" for the purposes of the said regulations.

(2) For the purposes of the said regulations the expression "pharmaceutical requirements" shall not include—

(*a*) Any preparation or substance (except insulin) that is prescribed in any medical prescription by reference to any trade-mark or trade-name or by reference to a particular maker; or

(*b*) Any serum, vaccine, or anti-toxin; or

(*c*) Any wine or spirituous liquor of a kind commonly sold by persons licensed to sell intoxicating liquors.

4. All drugs supplied by a contractor in accordance with the said regulations shall be required to conform to standards of quality in accordance with the following provisions, namely:—

(*a*) Where standards of quality are prescribed by any regulations for the time being in force under the Sale of Food and Drugs Act, 1908, those standards shall be complied with:

(*b*) In any other case, the standards (if any) prescribed in the British Pharmacopœia shall be complied with, and, where standards are not thereby prescribed, the standards (if any) prescribed in the British Pharmaceutical Codex shall be complied with.

5. (1) Fees (in addition to prices), to be computed as provided in the next succeeding clause, shall be payable out of the Fund for the compounding and dispensing of any pharmaceutical requirements and also for the containers in which any such requirements are supplied. The provisions of this subclause shall apply to authorize the payment of compounding and dispensing fees and of prices for containers for substances that are excluded from the expression "pharmaceutical requirements" by clause 3 (2) hereof.

(2) Any other fees that are authorized by the Rules for Prescription Pricing shall be payable to the contractor by the person to or for whom any pharmaceutical requirements are supplied.

6. (1) Subject to the provisions of subclause (3) hereof, the prices and additional fees to be paid for or in respect of pharmaceutical requirements supplied by contractors in accordance with the said regulations shall be computed in accordance with the provisions of clauses 5, 8, 9, 13 to 16, 17 (3), 18 to 21, and 23 to 25 (all inclusive), and the First, Second, and Third Schedules of the Rules for Prescription Pricing.

(2) Where any preparation or substance that is excluded from the expression "Pharmaceutical requirements" by paragraph (*a*) of subclause (2) of clause 3 hereof is supplied by a contractor under the said regulations he shall be entitled to receive from the Fund the amount that would have been payable if a preparation or substance of the same chemical definition (being a pharmaceutical requirement) had been supplied (but not exceeding in any case the sale-price of the preparation or substance actually supplied), and any excess of the price over the amount payable from the Fund shall be payable by the person to or for whom such preparation or substance was supplied.

(3) The prices and fees computed in accordance with the foregoing provisions of this clause shall be reduced by a discount of two and one-half per centum thereof.

(4) Nothing in this tariff or in the said regulations shall be construed to prohibit a contractor from charging a customer with the price of any goods, not being pharmaceutical requirements, that are supplied by him, or with the price of any pharmaceutical requirements that are supplied by him in excess of the maximum quantities hereinafter prescribed.

7. (1) Subject to the provisions of the next succeeding subclause, the quantity of any pharmaceutical requirements that may be supplied in accordance with the said regulations, pursuant to any one medical prescription shall not exceed—

(*a*) In the case of any drugs, medicines, or medicinal preparations that are prescribed to be taken in specified doses, a supply sufficient for a period of ten days commencing on the date of presentation of the prescription: Provided that where a prescription contains instructions that the supply prescribed therein is to be repeated, the supply may be repeated accordingly, but not on more than two occasions, and in any such case the aggregate quantities supplied shall not exceed supplies sufficient for thirty days' treatment, extending over a period not exceeding four months from the date of the presentation of the prescription:

(*b*) In the case of insulin prescribed for diabetic conditions, a supply sufficient for a period of four months commencing on the date of presentation of the prescription.

(2) On the recommendation in writing of the medical practitioner by whom any medical prescription is signed (whether such recommendation is given in the prescription or not) the Medical Officer of Health may, by an order in writing signed by him, authorize the supply of any pharmaceutical requirements in accordance with the medical prescription for definite or indefinite periods in excess of the periods specified in paragraph (*a*) or paragraph (*b*) of the last preceding subclause. Any authority given by the Medical Officer of Health for the purposes of this subclause may be given before or after the expiry of the original period.

8. For the purposes of clause 8 of the said regulations the substances or preparations hereinafter specified shall be deemed to be authorized midwifery pharmaceutical requirements, and may be supplied as follows:—

Description of Substance or Preparation.	Maximum Quantity for the Use of any One Patient.
Aspirin	25 × 5 grain tablets
Castor oil	2 oz.
Cyllin	4 oz.
Dettol or Pynol	4 oz.
Dettol cream	1 tube
Iodine, weak tincture of	2 oz.
Olive oil	4 oz.

Correspondence.

CONTINUOUS SPINAL ANÆSTHESIA.

SIR: We read with interest Dr. Joske's remarks on continuous spinal anæsthesia using "Novocain". We do not think it is necessary to use this method for spinal anæsthesia, and we have had great satisfaction with a single injection of two cubic centimetres of 10% "Metycaine". With this we have been able to perform all abdominal surgery, including cholecystectomy, ruptured peptic ulcer or gastrectomy. The method is much less complicated than continuous spinal anæsthesia, and it appears to us that it will last long enough to perform any abdominal operation.

Yours, etc.,

JOHN L. DEACON.
THOMAS F. ROSE.

Newcastle,
New South Wales,
May 30, 1941.

BRITISH MEDICAL ASSOCIATION ASSISTANCE TO MEMBERS ON MILITARY SERVICE, BRISBANE.

SIR: I do not want a prolonged discussion, but Dr. Alex. Marks is not correct. I did not propose that contributions should be called to the limit. I did draw attention to the fact that it could be done if such were necessary and the members (of the scheme) were in favour of it.

Dr. Marks's letter is apt to confuse, he writes of members: it must be realized that this means members of the scheme, not members of the British Medical Association, and the fact that only 130 members of the British Medical Association, even restricted to metropolitan and near members, were entitled to be present is evidence as to the truth of my statement that dissatisfaction with the scheme prevented members of the British Medical Association from becoming members of the scheme.

Members of the British Medical Association, as such, were not entitled to attend the meeting on May 16, nor to state their views.

Dr. Marks in his letter states: "It was evident from the discussion that some change in the allotment would probably become necessary"; this is surely confirmation of my statement.

In reference to my proposal at the November meeting, misquoted by Dr. Alex. Marks, the actual proposal was "that immediate consideration be given to the amendment of the manner of distribution of the funds raised under this scheme, giving full consideration to the urgent necessity for rendering all possible help to the British Empire, and the people thereof, during the present war". I hold my written notes for that meeting, and subsequent events, including Dr. Marks's letter in the journal of May 31, 1941, confirm the accuracy of my then expressed opinions. The scheme as at present conducted affords very meagre assistance to dependants of medical officers who may lose their lives on active service.

Yours, etc.,

ERNEST CULPIN.

Ballow Chambers,
Wickham Terrace,
Brisbane.
May 31, 1941.

SUICIDE AND ITS PREVENTION.

SIR: Dr. Derrick's article upon this subject is very stimulating and must call forth the admiration and gratitude of all good men and true, whether in the medical profession or not.

The Queensland Branch is to be congratulated upon having present the coroner, other public servants and members of the legal profession.

Dr. Derrick's thesis, so well expressed in the concluding paragraphs, should certainly be adopted by the medical profession as an aim to be achieved; but I think we should take more active measures to convert members of Parliament, those who administer our laws, and the legal profession to such ideals, which apply not only to suicide, but to divorce, illegitimacy, delinquency *et cetera*. The clergy also must be better educated in psychological medicine, as their help in appropriate cases is invaluable.

The greatest obstacle to progress is public opinion, which still holds that the suicide is a criminal and not a sick person—an obsolete concept which is still the determining factor in the action taken as regards burial by the official representatives of an important section of organized Christianity.

One way of promoting a better understanding of the mental unhealthiness underlying these morbid manifestations would be the introduction of a judicial instruction to coroners and other magistrates that in all such cases attempts must be made to obtain a privileged report from the medical attendant of the deceased or other abnormal person whose behaviour comes under the notice of the authorities. I have been astonished at a coroner giving a verdict in such cases, where the patient has been under treatment, without ever communicating with the medical practitioner concerned.

It is the duty of the medical profession to adopt the suggestions in the last two paragraphs of Dr. Derrick's article; but to put them into practice we need the cooperation of the parliamentarians, the legal profession, the police, and the support of the general public.

Yours, etc.,

A. M. DAVIDSON.

Al-Kasr,
Edgeware Road,
Enmore,
New South Wales.

June 1, 1941.

Obituary.

STEWART IRVINE WEIR.

WE are indebted to Dr. H. Boyd Graham for the following appreciation of the late Dr. Stewart Irvine Weir.

Stewart Irvine Weir, Captain, Australian Army Medical Corps, was killed in action in Greece on April 19, 1941. He was the only son of Dr. A. A. Weir, of Terang, Victoria, who was the President of the South-Western Country Subdivision of the Victorian Branch of the British Medical Association in 1937, and for several years he had been practising with his father at Terang.

Stewart was born at Deniliquin, New South Wales, in 1906, and was educated at Geelong Grammar School, Victoria, and later was in residence at Trinity College as a medical student, graduating M.B., B.S. (Melbourne) in 1930.

After being a resident medical officer at the Royal Melbourne Hospital he occupied a similar position for a year at the Children's Hospital. Later he went to England and became house surgeon at Oswestry Orthopædic Hospital, Shropshire, and in 1936 became a Fellow of the Royal College of Surgeons at Edinburgh.

He married Miss Margaret Douglas, of Edinburgh, and they have a little daughter, three years of age. He represented his subdivision on the Branch Council in 1939-1940, and resigned to go on the active list of the army.

Thus another very promising career has ended, a sacrifice to war in the cause of freedom. No one could have predicted that Australian lives would be yielded on the classic battlefields of ancient Greece in a struggle to protect our shores from a would-be conqueror of the world. We hope that Dr. Weir's sorrowing father and widow will be able in some sense to adopt the ancient Spartan's pride in the glory and honour of death in battle.

We are indebted to Dr. Julian Smith for the accompanying photograph.

Captain Hubert Smith, Australian Army Medical Corps, writes:

The news of the death of Stewart Weir while on active service in Greece will bring grief to all who knew him. "Stewey" he was known to his friends and beloved by them all. A gentle disposition and fine sense of humour claimed immense popularity for him among the troops. He was physically well endowed, tireless in his efforts, and as a medical officer of a field ambulance an ideal type—equally

successful with a regiment—quickly adaptable to any situation. My too brief friendship with Stewart will long be cherished. The Medical Corps is indeed proud to have had such men as Eric Bailhache and Stewart Weir.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 108, of June 5, 1941.

NAVAL FORCES OF THE COMMONWEALTH.

Royal Australian Naval Reserve.

Appointment.—William Dinwoodie Ackland-Horman is appointed Surgeon Lieutenant. Dated 15th May, 1941.

AUSTRALIAN IMPERIAL FORCE.

Australian Army Medical Corps.

Lieutenant-Colonel L. G. Male and Major K. C. Purnell, M.C., E.D., are appointed to command Australian Convalescent Depots, 9th April, 1941.

Captain (Temporary Major) G. T. Gibson relinquishes the temporary rank of Major, 31st March, 1941.

The undermentioned officers are transferred from Reinforcements from the dates shown: Captains R. T. Dalton, 7th August, 1940; L. P. Sapsford and D. S. Brandt, 10th August, 1940; and J. M. Bonnin and K. J. Friend, 30th August, 1940.

AUSTRALIAN MILITARY FORCES.

AUSTRALIAN ARMY MEDICAL CORPS.

Northern Command.

First Military District.

Major Q185269 A. J. Foote is apointed from the Reserve of Officers (A.A.M.C.), 30th June, 1940.

Captain R. Wallace is transferred to the Reserve of Officers (A.A.M.C.), 3rd Military District, 21st April, 1941.

The following officers are transferred to the Reserve of Officers (A.A.M.C.): Captains (Temporary Majors) D. H. K. Lee and S. Julius and relinquish the temporary rank of Major, and Captain G. S. Hayes, 4th April, 1941.

To be Captain (provisionally).—Harold Charles Wakefield, 29th March, 1941.

Reserve of Officers.—To be Honorary Captains—Norman Yates McCallum, Philip Scott Woodruff, and Robert Cecil Black, 16th April, 1941.

Eastern Command.

Second Military District.

Reserve of Officers.—The resignation of Honorary Captain G. Hagarty of his commission is accepted. *To be Honorary Captains.*—William McDonald, 9th April, 1941; William Wotherspoon McLaren, Francis Bathurst Halliday, 22nd April, 1941; James Herbert Carman, Adrian Grenfell Moffit, Gordon Marcus Brodie, Redvers Buller Shute, 23rd April, 1941.

Southern Command.

Third Military District.

Major J. M. Buchanan is appointed to command a Field Ambulance, 1st February, 1941.

Honorary Captains D. Pryde, M. F. A. Woodruff and W. Gove are appointed from the Reserve of Officers (A.A.M.C.), and to be Captains (provisionally), 30th January, 1941, 20th April, 1941, and 30th April, 1941, respectively.

To be Major (temporarily).—Captain C. L. Rosefield, 1st March, 1941.

Reserve of Officers.—To be Honorary Captains.—Charles Lloyd Coghlan, 16th April, 1941; Desmond Francis Lally and Edgar Lennard Roberts, 24th April, 1941.

Fourth Military District.

Honorary Captain F. R. Magarey is appointed from the Reserve of Officers (A.A.M.C.) and to be Captain (provisionally), 31st March, 1941.

To be Majors (temporarily).—Captains (provisionally) C. B. Sangster, J. L. Hayward, 18th March, 1941, and R. N. C. Bickford, 8th April, 1941.

Western Command.

Fifth Military District.

Honorary Captains M. Goldman and V. A. F. Stewart are appointed from the Reserve of Officers (A.A.M.C.) and to be Captains (provisionally), 31st March, 1941, and 10th April, 1941, respectively.

Reserve of Officers.—The resignation of Honorary Captain S. E. Craig of his commission is accepted, 11th March, 1941.

Seventh Military District.

Captain (Temporary Major) J. B. McElhone is appointed Assistant Director of Medical Services and is granted the rank of Lieutenant-Colonel (temporarily), 11th February, 1941.

CASUALTIES.

ACCORDING to the casualty list received on June 11, 1941, Captain E. V. Barling, A.A.M.C., of Stanmore, New South Wales, Captain J. W. McNamara, A.A.M.C., of Mosman, New South Wales, Captain N. H. Rose, A.A.M.C., of Sydney, New South Wales, and Captain F. G. Meyer, A.A.M.C., of Camperdown, New South Wales, previously reported missing, are now reported prisoners of war.

According to the casualty list received on June 12, 1941, Major B. Moore, A.A.M.C., of Bathurst, New South Wales, previously reported missing, is now reported prisoner of war.

According to the casualty list received on June 17, 1941, Captain D. N. F. Leake, A.A.M.C., of Canowindra, New South Wales, previously reported missing, is now reported prisoner of war. Captain P. C. Thomas, A.A.M.C., of Wembley, Western Australia, is reported missing.

Notice.

THE next clinico-pathological conference arranged by the Post-Graduate Directors of Medicine, Surgery and Pathology will be held in the lecture hall at the Prince Henry Hospital, Little Bay, New South Wales, on Monday, June 23, 1941, at 4.30 p.m. The subjects will be: (*a*) a case of abdominal emergency, for diagnosis and discussion; (*b*) a cerebral case, for diagnosis and discussion; (*c*) a fatal case of thyreotoxicosis. A cordial invitation to be present at the meeting is extended to all medical practitioners.

Honours.

BIRTHDAY HONOURS.

HIS MAJESTY THE KING has been pleased to confer the following birthday honours on Australian medical practitioners.

Dr. Frank Sandland Hone, of Adelaide, has been created a Companion of the Most Distinguished Order of Saint Michael and Saint George.

Dr. Albert William Shugg, of Hobart, has been created a Commander of the Most Excellent Order of the British Empire.

The congratulations of the medical profession are extended to Dr. Hone and Dr. Shugg.

Nominations and Elections.

THE undermentioned have been elected members of the New South Wales Branch of the British Medical Association:

Taylor, Hugh Carlyle, M.B., Ch.M., 1926 (Univ. Sydney), 27, Victoria Road, Bellevue Hill.

Seton, Miles Cariston, M.B., B.S., 1940 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Bundaberg Medical Institute. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

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